Epidemiological Features of Heavy Menstrual Loss and an Evaluation of Endometrial Surgical Techniques

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GLOSSARY

ANOVA	analysis of variance
CATH	conservative alternatives to hysterectomy
CI	confidence interval
ELA	endometrial laser ablation
DUB	dysfunctional uterine bleeding
GHQ	general health questionnaire
GnRH	gonadotrophin releasing hormone
GP	general practitioner
HADS	hospital anxiety and depression scale
Hb	haemoglobin
HRT	hormone replacement therapy
IUCD	intrauterine contraceptive device
MEA	microwave endometrial ablation
MISTLETOE	Minimally Invasive Surgical Techniques - Laser, End-Thermal Or Endoresection
MRC	Medical Research Council
NSAID	non-steroidal anti-inflammatory drug
PG	prostaglandin
PMS	pre-menstrual syndrome
RaFEA	radio frequency endometrial ablation
RCOG	Royal College of Obstetricians and Gynaecologists
SD	standard deviation
SDT	semantic differential technique
SF-36	short form 36
SPSS	Statistical Package for the Social Sciences
TCRE	transcervical resection of the endometrium
TURP	transurethral resection of prostate
UK	United Kingdom

Definition of terms as used in this thesis

1/ Dysfunctional uterine bleeding:-
abnormal blood loss, either regular or irregular, occurring from a uterus which on clinical examination is equivalent to or smaller than ten week pregnancy size and exhibits no endometrial atypia.

2/ Menorrhagia:-
heavy menstrual blood loss, either regular or irregular, as reported by the patient, which leads to medical consultation.

DECLARATION

I hereby declare that I personally conducted the work presented in this thesis, collected and analysed the data, and composed its presentation. Direct clinical supervision was afforded by Dr D.E. Parkin and methodological support by Professor Adrian Grant. Mr Andrew Garratt gave specific advice on the use and analysis of short form 36. Dr Christine Bain assisted in the data collection and operative procedures in the trial involving microwave endometrial ablation.

All quotations have been distinguished by quotation marks with sources acknowledged, whilst references are identified within the text by numerals in parenthesis and in full in the reference section. This work has not been submitted in any previous application for a degree.

The randomised trial comparing medical management with transcervical resection of the endometrium was undertaken whilst the author was employed as a Research Training Fellow within the University Department of Obstetrics and Gynaecology and the Health Services Research Unit, Aberdeen, between October 1994 and February 1996. The fellowship was awarded by the Chief Scientist Office of the Scottish Office Department of Health. The randomised trial comparing microwave endometrial ablation with transcervical resection of the endometrium was partly funded by Microsulis PLC. The opinions expressed are those of the author.

Kevin G Cooper

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AIMS

The management of women with heavy menstrual loss is a common problem for every gynaecologist yet there are wide variations in practice. Much of this has arisen through lack of both evidence based practice and a robust evidence base itself. The work contained in this thesis aims to determine baseline epidemiological information on women referred from primary care with menorrhagia and also to evaluate endometrial ablative surgical techniques in the context of randomised trials. This will hopefully contribute to the evidence base to which we should continually add, and base our practice upon.

It was felt necessary to perform a survey of all women who were first time referrals with heavy menstrual loss to the gynaecology outpatient department over one year. The socio-demographic and epidemiological features of this population including their preferences regarding management, expectations, and also an assessment of their quality of life would be ascertained. This was considered to be essential baseline information. These data are not available for the Grampian or Scottish population and it was felt that the results should enhance the generalisability of the randomised trials undertaken in this thesis. The data will also serve as a benchmark for auditing changes over time with the implication of new information and guidelines on the management of women with heavy menses.

Endometrial ablative techniques had been previously compared with hysterectomy as potential alternatives to this procedure for women with menorrhagia. The satisfaction rates achieved were high (around 80%), but significantly lower than for hysterectomy, which also guaranteed amenorrhoea. Recommendations were made that ablation should only be offered once medical management of menorrhagia had failed. A randomised trial comparing transcervical resection of the endometrium

against traditional medical treatment for women complaining of heavy menstrual loss was undertaken. This set out to establish satisfaction with and acceptability of the two forms of management, effects on menstrual symptoms and health related quality of life, and subsequent additional management required. Follow-up was planned in the short-term, at four months and medium term at two years.

This trial was felt necessary to establish the true place of endometrial ablative techniques in the management of menorrhagia, to evaluate the effectiveness of present medical regimes and to determine what additional treatments are required. Importantly the trial was designed to be pragmatic. This determined that normal clinical practices were to be followed for general practitioner referral and patient assessment. Investigations which were not part of the standard patient assessment (e.g. ultrasound or diagnostic hysteroscopy), were also avoided. In addition, medical treatments prescribed were at the discretion of the consultant to whom the women was referred, and not a specific medication in a pre determined dose/ timing. The pragmatic approach, through reflecting normal practice should enhance the external validity of the results, by maximising recruitment of a diverse population of women with dysfunctional uterine bleeding. However, pragmatism can only to serve to demonstrate differences and cannot explain why they occur.

The second randomised trial was undertaken to formally evaluate a "new generation" ablation endometrial ablative technique, microwave endometrial ablation. Microwave ablation has been described as a simple fast and safe technique for destroying the endometrium, but has never undergone rigorous evaluation. A randomised trial comparing it with the gold standard procedure, transcervical resection of the endometrium, was undertaken. Outcomes in terms of patient satisfaction, acceptability and changes in menstrual status and quality of life

after four months were determined. Operative parameters were also measured including operating and recovery times, complications and analgesia requirements. As traditional hysteroscopic surgical techniques are technically difficult procedures, proving satisfactory outcomes for a potentially simple and safe procedure has important implications for both gynaecologist and patient. If shown to be safe and effective, microwave ablation could be undertaken in the outpatient setting using local anaesthesia, freeing valuable theatre space and anaesthetists.

Recommendations based on the findings from these studies can be made. Undertaking this work, including the background reading should also uncover areas that require further investigation, and these will also be discussed.

Summary of aims

1/ To determine characteristics of women in Grampian district referred to the gynaecologist with heavy menstrual loss in the context of:-

a/ socio-demographic data

b/ epidemiological features

c/ patterns of G.P. referral and treatment

d/ treatment preferences and expectations

e/ effect of menorrhagia on health related quality of life

2/ To compare transcervical resection of the endometrium with traditional medical treatments for women first referred to a gynaecologist with heavy menstrual loss. This is to establish the role of endometrial ablation in the management of this condition. Outcomes were determined by measuring at four months and two years with particular reference to:-

a/ patient satisfaction and acceptability of treatment

b/ changes to menstrual status

c/ changes to health related quality of life

d/ additional treatments required

3/ A new generation endometrial ablative technique, microwave endometrial ablation was compared in a randomised trial with transcervical resection of the endometrium to establish its effectiveness in terms of:-

a/ patient satisfaction with and acceptability of the procedure

b/ change in menstrual symptoms

c/ changes to health related quality of life

d/ operative data

e/ recovery times and return to work

ABSTRACT

The research described in this thesis endeavours to rationalise certain aspects of the secondary care management of women with heavy menstrual loss, in particular the place of endometrial ablative surgery. The work was undertaken in a gynaecology department with an established record in research evaluating endometrial ablative techniques. The hospital is the regional referral centre for all women with menstrual disorders, hence a centralised and stable study population was available.

Chapter 1 outlines the aetiological and known epidemiological factors for dysfunctional uterine bleeding. A review of the medical treatment options for menorrhagia is undertaken. The equipment requirements and techniques of transcervical resection of the endometrium (TCRE) and microwave endometrial ablation (MEA) are described. The randomised controlled trials evaluating TCRE that have been published to date, are discussed and critically reviewed.

Chapter 2 presents the patterns of referral, socio-demographic and clinical details, primary care treatment, and effect on health related quality of life of women referred to this centre, over one year with heavy menstrual loss. Issues of treatment preference and expectations of treatment were also explored. 273 women were referred for the first time with heavy periods making up 7% of new gynaecological referrals to Aberdeen. 21% had their complaint for less than one year. 64% of women were disabled for more than two days per cycle, despite 78% having received treatment from their general practitioner. The women as a group exhibited a significant reduction in all dimensions of health related quality of life. 31% of women had a strong treatment preference and they differed from women with no preference. Those preferring medical treatment were less restricted by their menstrual problems, fewer had been treated previously by their GP, and they had

near normal quality of life levels. Those preferring TCRE were more likely to have completed their education by age sixteen, had all tried medical management, and had a greater desire for amenorrhoea.

Chapter 3 describes the subjects, methods and outcomes at four months of a prospective randomised comparison of medical management with TCRE for women with heavy menstrual loss. Women allocated medical treatment were significantly less likely to be totally or generally satisfied (27% versus 76%), to find the treatment acceptable (36% v 93%), and would be less willing to have the treatment again (31% v 93%). Although pain and bleeding were significantly improved by medical treatment, the reduction was modest in comparison with TCRE. Haemoglobin levels were significantly increased only following TCRE. Quality of life scores improved in both trial arms, although only transcervical resection returned them to normal values

Chapter 4 outlines the clinical and quality of life outcomes at two years for the randomised trial of medical treatment versus TCRE. Women allocated medical treatment were significantly less likely to be totally or generally satisfied (57% v 79%), to find their management acceptable (77% v 93%), or to recommend their allocated treatment (24% v 78%). 59% of women in the medical cohort had undergone TCRE, hysterectomy or both, whereas 17% in the TCRE cohort had undergone further surgery. Bleeding and pain scores were similar in the groups and highly significantly better than at recruitment. Quality of life scores were significantly improved from baseline for five of the eight health scores in the medical arm, and seven in the TCRE arm.

Chapter 5 describes the subjects and methods for a prospective randomised controlled trial comparing MEA with TCRE. Operative details and outcomes at four months are presented. MEA was a significantly faster technique than TCRE (11.4 v 15 minutes). Postoperative stay was less with microwave, though not significantly so, and analgesia requirements were low and equivalent (< 30%) for both techniques. Satisfaction rates were slightly lower following MEA (74% v. 81%), whilst acceptability of treatment rates were equivalent (92% v 94%). MEA lead to more significant improvements in health related quality of life measurements than TCRE.

Chapter 6 concludes that:- Primary care management guidelines need to be implemented, whilst treatment preferences and expectations should be established prior to deciding on treatment. Quality of life measurements should be used to determine degree of debilitation and to ascertain treatment success. Medical treatment was less effective than TCRE, irrespective of previous treatment or type of medical management received. Early recourse to endometrial surgery should therefore be considered, with the choice made by the woman after discussing the advantages and disadvantages of all the therapeutic options. MEA was shown to be a quicker technique than TCRE, which is equally effective, and is also simple to learn.

Areas for future research include: identification of an acceptable and accurate method of measuring menstrual blood loss, the search for a medical treatment effective in the long term, the assessment of ablative surgery under local anaesthesia in the out patient setting and investigation of immunological therapies such as antibodies to specific endometrial factors.

Chapter 1

Heavy Menstrual Loss:
aetiology, epidemiology, and management options

an overview and critique of the literature

INTRODUCTION

This thesis will attempt to clarify the place of endometrial destructive surgery in the management of heavy menstrual loss. Randomised studies have shown transcervical resection of the endometrium and endometrial laser ablation to be effective alternatives to hysterectomy for the treatment of menorrhagia, but no trials exist comparing medical management with transcervical resection of the endometrium. Descriptions of alternative endometrial ablative techniques which are simple to undertake, and quick to perform are appearing more commonly in the literature. Few have been evaluated in the context of a randomised controlled trial.

In this chapter current aetiological and epidemiological factors pertinent to menstrual dysfunction are considered, followed by a review of traditional medical therapies. The development of endometrial surgical techniques is traced and the mechanisms of action of electrodiathermy and microwave technology described. The preparation, equipment and techniques utilised for these surgical procedures will be outlined next. Finally, a critical review of published studies evaluating endometrial surgical techniques for heavy menstrual loss is undertaken in order to highlight the need for prospective randomised controlled trials in this area.

Chapter 1 is subdivided as follows:

1.1 menorrhagia:- aetiology and epidemiology

1.2 medical management of heavy menstrual loss - a critical review of the literature

1.3 development of endometrial surgical techniques

1.4 mechanisms of action of electrodiathermy and microwave

1.5 requirements for endometrial surgery (equipment, preparation and techniques)

1.6 The place of endometrial surgery in the management of heavy menstrual loss - a critical review of the literature

1.1 Menorrhagia: - aetiology and epidemiology

1.1.a - aetiology

The mechanisms governing the control of menstruation and in particular, severity of bleeding are poorly understood. An interplay of a number of factors control menstruation which are "local" uterine, rather than hypothalamic-pituitary in origin. Vascular spasm of the endometrial spiral arterioles, local uterine haemostasis / fibrinolysis, and endometrial regeneration all contribute to the mechanism of menstruation. Defective haemostasis may result from a breakdown of these resulting in excessive blood loss, which, in the absence of demonstrable pathology, is called dysfunctional uterine bleeding.

Menstruation is preceded by intense vasoconstriction of the spiral arterioles(1). This is followed by a period of relaxation for 4 to 24 hours, during which time the majority of endometrium is shed. A return of intense vasoconstriction is probably

the principal haemostatic event, rather than platelet-fibrin plug formation(2). Endothelin-1 may directly, or by causing production of prostaglandin $F_2\alpha$, exert local control on the endometrial vascular bed, causing this intense vasoconstriction seen immediately prior to menstruation, and also may be required in the cessation of menstruation(3). Endometrial proteinases and tissue factor may contribute to systemic factors to control the mechanisms of regulation of tissue dissolution, tissue shedding, and vascular bleeding during menstruation(4). This paracrine response could be further mediated by nitric oxide which is a potent vasodilator and inhibitor of platelet aggregation through initiation and control of menstrual bleeding(5). Uterine bleeding can be triggered in the menstrual cycle by dropping progesterone levels, regardless of oestrogen levels(6). A drop in progesterone levels also initiates inflammatory mediators and an influx of monocytes which may be essential to endometrial shedding(7), implying a pivotal role for this hormone.

Menstruation, has many hallmarks of an inflammatory process in which the cascade of events involving the interaction between the stroma-epithelial cells of the endometrium and the lympho-haemopoetic cells are utilised to reject, remodel and regrow the endometrium each month(8). Mast cell regulation of human endometrial matrix metalloproteinases which lead to focal menstrual breakdown(9), and the aforementioned leucocyte infiltration pre-menstrually(7) both support this. Endometrium also has its own fibrinolytic system and there is evidence that excessive fibrinolytic activity may cause dysfunctional uterine bleeding(10,11). However, one study comparing women with normal and pathological blood loss, little differences were found in fibrinolytic products(12).

Little is known about the factors which govern endometrial regeneration, although local oestrogen effects, epidermal growth factors, prostaglandins(8), and endothelins are all felt to contribute. Local hypoxia causes vascular endothelial growth factor to increase in the endometrium which may be a stimulus to endometrial regrowth(13), whilst an interaction of many growth factors which predispose to endothelial proliferation and angiogenesis have been demonstrated(14). The mitogenic actions of endothelin may also play a role in endometrial regeneration and remodelling, particularly following menstruation(3). Breakdown in this regenerative process could also play a role in defective menstruation.

Prostaglandins seem to play an integral role in the pathogenesis of dysfunctional uterine bleeding(8,15-18). Prostaglandins E_2, D_2 and prostacyclin are vasodilators, whilst prostaglandin $F_2\alpha$ and thromboxane A_2 are vasoconstrictors. Platelet aggregation is also promoted by thromboxane A_2 and inhibited by Prostaglandin D_2 and prostacyclin. An imbalance in the production or potency of prostaglandins from these two groups, in favour of vasodilation, has been demonstrated in women with excessive menstrual loss(19). The role of prostaglandins in menstrual dysfunction is further compounded by the fact that non steroidal anti-inflammatory drugs, which inhibit prostaglandin synthesis, are effective in reducing menstrual flow in women with pathological menstrual blood loss(20-25). Prostaglandin production by the endometrium is influenced by changing levels of oestrogen and progesterone; withdrawal of progesterone enhances prostaglandin synthesis(26). Other postulated mediators of endometrial function include leukotrienes, and

endothelins. Whereas no correlation with leukotriene function and disordered menstruation has been demonstrated, endothelin-1 is a potent vasoconstrictor, found in the endometrium. Endothelin is reduced in glandular epithelium in women with menorrhagia, and does not exhibit the same cyclical variation(27).

One definition of menorrhagia is "menstrual bleeding lasting for longer than seven days or blood loss exceeding 80mls from normal secretory endometrium after normal ovulation"(American College of Obstetricians and Gynaecologists, 1982). 80mls blood loss per cycle represents the 95th percentile, with a mean between 30 and 40 mls, based on large population studies(28,29). Menstrual history is an unreliable method for truly determining whether blood loss is pathological; only 11 to 13% of women complaining of menorrhagia have menstruation lasting more than seven days(30,31), and 62% have objectively measured blood loss of less than 80mls/cycle(31). As 92% of blood loss occurs in the first 3 days, duration of menstruation has little influence on total menstrual blood loss(32). 60 mls / cycle blood loss has been proposed as a more sensible value as iron deficiency anaemia can occur at this level(28,33). Even at this lower cut off, 40% of women with subjective menorrhagia will lose less than this amount(31). Objective menstrual blood loss measurement is a laborious and specialised task not suited to everyday clinical practice. Unfortunately, alternative, non laboratory methods for estimating blood loss such as tampon / pad counting and weighing are unreliable(30), although pictorial blood loss assessment charts seem to have a sensitivity and specificity of above 80%(34). In everyday practice it is usual to offer reassurance, advice and if necessary treatment based on history, clinical experience and an estimation of how much the women's quality of life is affected by her change in

menstruation. Only rarely is an objective estimation of menstrual blood loss undertaken outwith the context of clinical trials. In this thesis "menorrhagia" is a subjective increase in menstrual blood loss, either regular or irregular, which has led the woman to consult with a doctor. Similarly, the term dysfunctional uterine bleeding, when used in this thesis, pertains to abnormal blood loss, either regular or irregular, occurring from a uterus which on clinical examination is equivalent to or smaller than ten week pregnancy size and exhibits no endometrial atypia.

The majority of menorrhagia, about 80%, is idiopathic in that there is no demonstrable causal pathology; this is described as dysfunctional uterine bleeding(35). The most common known and postulated causes or factors which contribute to heavy periods are

1/ pathological:-

fibroids, adenomyosis, endometrial hyperplasia, hypothyroidism and platelet disorders such as Von Willebrands disease.

2/ iatrogenic:-

intauterine contraceptive devices

3/ other associated factors

genetic, parity and obesity

The proportion of pathological causes of menorrhagia will obviously be determined by how rigorously they are sought. Standard practice would include a general examination to exclude thyroid disease and bleeding diatheses in combination with a pelvic assessment and endometrial biopsy(36), but will undoubtedly miss some

identifiable causes of menorrhagia. Hormonal screening for polycystic ovarian syndrome and hypothyroidism should not be undertaken routinely, and there is good evidence that dilatation and curettage (D&C) is neither therapeutic(37,38), nor effective in excluding intrauterine pathology(39,40). Also, the use of D&C for excluding endometrial carcinoma is not cost effective in women less than 40 years old because of the very low prevalence(37). Despite this, D&C remains one of the commonest operative procedures performed on women in Britain(41). Out-patient endometrial biopsy, which is well tolerated and similarly effective in sampling the endometrium, should replace D&C in the vast majority of cases(36,42-44). There is no doubt that hysteroscopic evaluation of the uterine cavity will increase the chances of identifying intauterine pathology(45,46), but we await evidence from randomised controlled trials as to how this effects subsequent treatment and outcomes for these women.

1.1.b - epidemiology

A complaint of excessive menstrual blood loss is one of the commonest reasons for referral to a gynaecologist accounting for 12% of new appointments(47). It has been estimated that 30% of women will complain of excessive menstrual loss at some time(29,48). At primary care level, consultation rates for heavy periods have been estimated at between 20.4(35) and 30.7 per 1000 women (Royal College of General Practitioners, 1986), with up to a third of these referred on to secondary care(49). If women in the age group spanning 30 to 49 years are selected from England and Wales, then 5% of women consult their general practitioners for excessive menstrual blood loss each year(50). In 1993 this amounted to 822,000 prescriptions,

40,000 hysterectomies and 10,000 endometrial ablative procedures all as treatment for excessive menstrual loss(51).

Of women referred to a gynaecologist with a complaint of excessive menstrual loss, only 40% will have true menorrhagia, >80mls/cycle blood loss(30,31). Despite this, a large number end up having surgical treatment. 60% of women had undergone hysterectomy within five years of gynaecological referral with heavy periods in one population study(49). What is known, is that as a group, women with a subjective complaint of heavy menstrual loss do suffer a significant reduction in health related quality of life, as measured using the health survey questionnaire short form 36 (SF-36) (52,53), (Appendix 1a). Few studies have evaluated health related quality of life following treatment, those undertaken demonstrate a greater improvement in those treated surgically rather than medically(54), and similar global improvements for transcervical resection of the endometrium and hysterectomy(55).

The likelihood of menorrhagia has been shown to increase significantly with age over 40 years. Parity, smoking and body mass index have no significant effect once corrected for age(56). A genetic link has been postulated, as have associations with smoking, diet and body mass index. Psychiatric illness and psychological features have also been associated with menstrual disorders, initially by the ancient Greeks who blamed abnormal behaviour and mental instability on the uterus, hence the term "hysteria". More recently, the converse is acknowledged, that anxiety and depression can manifest as menstrual problems in a proportion of women. This has been shown in population studies, especially of women undergoing hysterectomy(57,58).

There is strong evidence that consultation rates for menstrual problems are rising, a 73% increase in consultations was noted by the Royal College of General Practitioners from 1971 and 1981 (RCGP, 1986). There has been a steady increase in surgical treatment for these conditions, particularly for endometrial ablative techniques(59,60). There is also wide national and international variation in hysterectomy rates(61). Increases in rates of surgery cannot simply be explained by an increase in pathological bleeding. A number of theories which all essentially hinge around the changing role of the female in the western world have been postulated. The term "menstrual intolerance" has been coined to describe those women who have completed their families who now regard menstruation as an unnecessary nuisance. The increasing consultation rates may also reflect a media derived awareness that simpler treatments or techniques are available which might improve menstrual symptoms.

There is a paucity of national data regarding patterns of referral for treatment, treatment preferences, expectations of treatment and sociodemographic features of women with heavy menstrual loss. What little there is has centred on a population in one regional health authority of England, Oxford, and concentrates principally on primary care(49,62,63). One study demonstrated that 43% of women with menorrhagia were referred to a gynaecologist within a month of seeing their general practitioner and that 45% had not been prescribed medical treatment(49). Another that 36% of women referred to the gynaecologist had a treatment preference(63). Many experts have argued that patient preference should be an important guide to treatment choice, and may strongly influence outcome success(23,35). Care must be taken however when extrapolating statistics based on

the population surrounding Oxford to other parts of the UK which may not have similar populations. Ideally epidemiological data should be available from the geographical area of the population under investigation.

1.2 medical management of heavy menstrual loss

Treatment of menorrhagia has two related goals: to control menstrual blood loss, either by reducing or stopping it altogether, and to improve quality of life(51). When a demonstrable pathology is present, specific treatment of this is indicated. The majority of women however, have dysfunctional uterine bleeding and for them medical therapy is traditionally regarded as the first line treatment of choice. The choice of therapy is dependent on the age of the patient, their current need for contraception, the side effects which may be experienced whilst receiving therapy and actual cost(64). In addition proven long term efficacy of the chosen drug, safety, and acceptability(23) should be included. These factors have not been adequately established for the majority of non surgical menstrual treatments, with most trials concentrating on reduction in objective menstrual blood loss and for under six months follow-up. The management of women with heavy periods by their general practitioner should improve and become standardised following the introduction of the Royal College of Obstetricians and Gynaecologist guidelines regarding management the of menorrhagia in primary care(65).

Drug treatments can be broadly divided into non-hormonal treatments taken perimenstrually, and hormonal, which are used continuously or for varying duration throughout the cycle. Within these two groups are individual treatments

which have different modes of action, and they will be discussed individually under the two headings.

1.2a Non-hormonal drug treatment

Non steroidal anti inflammatory drugs (NSAID's)

The role of prostaglandins has been discussed in the previous section, aetiology and epidemiology of menorrhagia. NSAID's certainly inhibit the production of prostaglandins, although different NSAID's give varying responses not only in level of inhibition, but also between different organs(66). The fenemates, of which mefenemic acid, is the most widely known, may also act by inhibiting binding of the vasodilator, PGE2(67). One randomised controlled trial measuring objective menstrual blood loss demonstrated mefenemic acid to be more effective than non-fenemates(68). Mefenemic acid is most effective in reducing menstrual loss when it is pathological(24). Used in a dose of 500mg three times daily for the first five days of the menstrual cycle results in a reduction of menstrual blood loss ranging from 22% to 46%(22-24,68,69). This was the regime used in this thesis for women prescribed these drugs. Dysmenorrhoea can be effectively treated by mefenemic acid, with symptomatic relief in up to 70% reported(23,24). Side effects can occur in up to 30% of patients and acceptability of treatment was assessed as 31% by patients(23). The only follow-up longer than one year shows a sustained effect on mean blood loss reduction at over one year of 35%.

Tranexamic acid

There is evidence that excessive fibrinolytic activity is a cause for dysfunctional uterine bleeding(10,11), although one study comparing women with normal and

pathological blood loss, little differences were found in fibrinolytic products(12). Tranexamic acid, an anti-fibrinolytic agent has been shown in many randomised trials to significantly reduce menstrual blood loss from between 36% to 54%(20,70,71), including for women with intrauterine devices(72). None of these studies evaluate the treatments beyond six months and report drop-out rates between 10% and 20%, but with low rates of side effects, and a 77% acceptability rate in one trial(20). It is the drug of choice in Scandinavian countries for menorrhagia where hysterectomy rates are 50% lower than the UK(20). Recommended dosage is 1g six hourly for the first three to five days of menstruation. In this thesis, if tranexamic acid was prescribed it was in a dose of 1g four times a day for the first five days of the period. Concerns regarding increased risks of thrombo-embolic phenomena, which limited its use in the UK are unsubstantiated, with rates equivalent to the normal population(73). Tranexamic acid is certainly an effective medical treatment for women with pathological blood loss, but there is a paucity of evidence on long term treatment, continuation rates and quality of life improvement.

Ethamsylate

The exact mode of action of this drug in the treatment of menorrhagia remains obscure, but is thought to be through capillary stabilisation and haemostasis. Early trials suggested very effective (50%) reductions in menstrual blood loss for women with true menorrhagia(74). More recent larger randomised controlled trials have shown a more modest reduction of 20%(75), and the largest trial failed to show any beneficial effect(20). Dosage is 500mg, six hourly, for the first five days of the menstrual cycle. Side effects were reported in 10 - 16% of cases with short term

discontinuation in 20 - 30% of the above studies. In the largest study, only 33% were prepared to continue with ethamsylate after completing the trial at four months(20). There is no evidence to support its use in the dose and timings presently recommended(65), and this drug was not prescribed to any women in studies undertaken in this thesis.

1.2b Hormonal drug treatment

The potential advantages of hormonal therapy for women with problematic menses are that the cycle can be regulated or prolonged if necessary, whilst the severity of the bleeding reduced. The disadvantages of hormonal treatment are their extended use through the menstrual cycle and possible side effects.

Combined oral contraceptive

Combined oral contraceptives, apart from inhibiting ovulation, induce endometrial atrophy which is the probable mode of action for reducing blood loss. Reductions in menstrual blood loss of 43% - 53% have been reported in randomised controlled trials involving women with menorrhagia(68,76). As contraceptives, these drugs have good long term compliance records, but this has not been established for the management of menstrual disorders. The newer, low dose preparations which are more suitable for the woman over 35 years of age, have been evaluated in a small cohort of twenty women and significantly reduced both duration and severity of bleeding(77). Combined oral contraceptives containing the progestogens desogestrol and gestodene should be avoided in women who have an increased risk of venous thromboembolism (Committee on Safety of Medicines 1998). Combined

oral contraceptive pills prescribed in this thesis were 30 microgram ethinyl-oestradiol, second-generation progestogen preparations.

Progestogens

Oral norethisterone is the most commonly prescribed drug for the treatment of menorrhagia in the UK(51). Studies assessing its use in objectively proven, ovulatory menorrhagia have shown it to be of little value at the doses and timings used(21,78). From these results other researchers have made sweeping generalisations stating that progestogens are the least effective treatments for menorrhagia(20,51). All that can be stated from these trials is that progestogens used for 7 - 10 days in the luteal phase are useful only for regulating an irregular cycle or to cause a predictable withdrawal bleed. Progestogens are known to cause amenorrhoea if used continuously at high dosage, and a small trial had shown effective reduction in menstrual blood loss for women with ovulatory and anovulatory menorrhagia(79). The recent publication of a randomised controlled trial with larger numbers which has definitively proven that oral norethisterone used in a dose of 5mg three times a day from day 5 - 25 lead to a 87% reduction in objective menstrual blood loss(80), has reinstated its position in the treatment armamentarium. However, despite the highly significant reduction in blood loss only 44% found the treatment acceptable and only 22% would continue using it. Although short cycle progestogen treatment maintains a secretory endometrium, long cycle, as used in the above study actually leads to endometrial atrophy, which undoubtedly serves to cause effective reduction of blood loss. Those prescribed progestogens in this thesis received either norethisterone 5mg three times a day, or

medroxyprogesterone acetate 10mg twice daily, from days 5 to 25 or 12 to 25 of the cycle.

Progestogens used locally, on intrauterine contraceptive devices also result in profound endometrial atrophy, leading to highly significant reductions in menstrual blood loss(80,81). Additional advantages are reversible contraception and improved compliance as replacement need only be every five years. Systemic side effects are reduced as a small dose of progestogen acts locally with little systemic absorption, however problematic breakthrough bleeding can occur in the first six months. Recent studies have shown a reduction of women on a hysterectomy waiting list using a levonorgestrol intrauterine contraceptive device(82), and a randomised controlled comparison with transcervical resection of the endometrium achieving high (84%), but slightly lower satisfaction rates and equivalent scores for health related quality of life(83). This last trial unfortunately did not have sufficient power to show meaningful differences in any parameter other than menstrual blood loss between the two treatments. The Mirena intrauterine system was not a management option for women in this thesis as it was not licensed for the treatment of menorrhagia.

Danazol

This drug is a testosterone derivative, which through a variety of direct and indirect mechanisms, induces endometrial atrophy(84). Its effectiveness in reducing menstrual blood loss has been demonstrated in a number of randomised controlled trials(11,23,85-87). A significant proportion become amenorrhoiec and overall reductions in blood loss of 60% - 80% can be expected. Danazol has also been

shown to reduce the number of bleeding days and to have a carry over effect with significant reductions in blood loss continuing three months after stopping treatment(88). Side effects including weight gain, headaches, musculoskeletal pain and acne are experienced by over 70% of users(23,87), and this, along with its cost make it unsuitable for long term use. Danazol was not used as a first line treatment for women with heavy menstrual loss in this thesis, but when used it was prescribed at 200mg a day for ninety days continuously.

Only one drug trial has evaluated effect in the medium to long term(15), and none have measured changes in health related quality of life, or adopted a pragmatic(89,90) approach to there use in everyday practice. These are major deficiencies when investigating such a common and debilitating complaint. The need to rectify this, and to identify and compare the most effective medical treatments with each other, and with conservative surgical techniques, have been stated in the literature(51,91).

1.3 the development of, and types of endometrial surgical techniques

The development of hysteroscopic surgery is attributed to Pantaleoni(92) who in 1869, visualised a uterine polyp through a straight endoscope and cauterised it. During the 1900's modified cytstoscopes were more frequently used for diagnostic procedures, but it was not until the 1960's, with the advent of fibre optic technology, which provided good illumination, that hysteroscopic views became reliable. In the 1970's uterine distension media improved the view further and paved the way for operative hysteroscopic procedures. Electro-resection of the endometrium was described by Neuwirth and Amin in 1976(93) for the removal of

submucous fibroids. De Cherney and Polan performed myomectomies using an unmodified urological resectoscope in 1983(94) and later, successful resection of the endometrium in a series of 21 women in 1987(95). The first UK results were presented by Magos in 1989(96) who called the procedure transcervical resection of the endometrium (TCRE). Other exponents of electrocautery proposed a technique of rollerball coagulation / ablation of the endometrium, rather than resection, and reported high rates of satisfaction with outcome(97-99). In the early 1980's, Goldrath pioneered an alternative effective method of endometrial ablation using a laser fibre, under direct vision, down a hysteroscope(100). Davis reported his series of laser ablations in the UK in 1989(101). Following observational, series reports(102,103), a number of randomised controlled trials were undertaken in the 1990's. These compared transcervical resection of the endometrium and / or laser ablation with hysterectomy(104-108), and one has compared the two endometrial procedures(109). These will be discussed later.

Hysteroscopic endometrial surgical techniques, although effective, require a lot of training and skill to become proficient at them. A number of "blind" endometrial destructive procedures, utilising various energy sources have been developed, which claim simplicity of use, and have been reported in the literature. These ablative techniques include, radio frequency-induced endometrial ablation (RaFEA)(110), the uterine thermal balloon(111), cryoablation(112), photodynamic therapy(113) and microwaves(114). All report high levels of success, but none have been rigorously evaluated in the context of a randomised controlled trial. Later in this thesis, the results from the first comparative randomised controlled trial of

transcervical resection of the endometrium versus microwave endometrial ablation will be presented.

1.4 mechanisms of action of electrodiathermy and microwave ablation

Endometrium has extraordinary regenerative powers if the basal layer is left in tact(115) therefore, if endometrial destructive techniques are to be successful, endometrium and endometrial glands must be destroyed. These glands may extend up to 3mm into the myometrium, therefore this must also be removed or destroyed to be effective in preventing regeneration(116). The depth of destruction must not disperse much beyond this depth as the myometrium at the cornual regions may be only 4 - 6 mm in depth(117).

The mechanisms of action of the two endometrial surgical techniques used in the trials described in this thesis are outlined here.

1.4a - Elecrodiathermy

Transcervical resection of the endometrium is the principal endometrial surgical procedure used in the UK(59,118) and utilises electrodiathermy as the energy source. Modern electrosurgical generators utilise a primary oscillator circuit to generate a basic electrical wave frequency of 475 - 750 kHz. In cutting mode, this sinusoidal waveform is amplified, but otherwise unaltered to produce a continuous output. Coagulation or blend modes are produced by modulation of the reference signal through an electronic gate using a burst oscillator, which produces an

interrupted waveform. This results in a low frequency (22 - 33kHz), high voltage output.

During monopolar electrosurgery, as used in transcervical resection of the endometrium, this electrical current passes down the active electrode (cutting loop) to a passive electrode, and back to the generator. This initially high frequency electrosurgical energy can be modified, as described above, to achieve certain actions within tissues. Resection with a cutting loop or coagulation with the rollerball can both be utilised within the uterus and often a combination of the two is used in clinical practice. The ultimate tissue effect is mediated through the production of local heat(119). Focused, high frequency heating to high temperature (100 - 1000°C) leads to mechanical injury and produces an incision through complete tissue vaporisation; cutting mode. Less focused, low frequency heating to lower temperatures (45 - 100°C) has a coagulative effect due to desiccation and denaturation of protein; coagulation mode.

Detailed studies on the effects of electrosurgery on uterine tissue have been undertaken in vitro and in vivo by Duffy et al(117,120). In vitro cutting mode electroresection resulted in a narrow zone of thermal necrosis (ZTN) which did not vary with power output, but was related to duration of exposure. In vitro coagulation mode desiccation resulted in a depth of destruction of 3.24 - 3.49 mm that did not vary with power output or duration of exposure. In vivo, these findings were confirmed for both cutting and coagulation modes. Although clinically significant thermal transmission through the uterus could not be shown, prolonged application of an activated electrode for more than five seconds in the

same area could be dangerous. The use of desiccation mode in the cornual region was felt to be safer because of its more consistent ZTN and hence lower risk of perforation than with the resection loop.

Loop resection of the endometrium can be undertaken using a pure cut, or blended mode for additional haemostasis. Power settings vary between 80 - 120 Watts, with 100 Watts generally recommended(121). The optimal electrical setting for rollerball ablation has not been established and all three modes, cutting, coagulation or blend can be used. Power settings are lower than for loop resection, varying between 40 - 100 Watts(97).

1.4b - Microwave

Microwaves are electromagnetic waves with a wavelength of 0.3 to 30 cm and frequency, 300 to 300 000 MHz (between radiowaves and infrared radiation). A 9.2 GHz microwave frequency was determined to be the most effective at producing the 5mm depth of necrosis necessary to completely destroy the basal layer of the endometrium. A microwave generator, or magnetron, supplies microwave energy to a hand held applicator. The applicator is an 8mm diameter, 15cm circular metal pipe with a dielectric filled waveguide to propagate microwave energy at 9.2 GHz into the uterine cavity. The dielectric extends beyond the tip of the pipe to form the radiating tip. With power levels of 30 Watts, energies of 1.5 - 9.3 kJ result and a hemispherical field pattern emanates from the dielectric tip, which if placed in egg white, causes a symmetrical ball of coagulum of constant thickness. Extensive testing on animal tissue, excised perfused uteri and pre-hysterectomy in vivo

specimens have been undertaken and a depth of necrosis of 5 - 6 mm can be consistently achieved.

Uterine tissue has a very high water content so the microwave field amplitude is reduced by about 90% approximately 3 mm from the surface of the applicator tip. Beyond this zone of intense microwave heating, further tissue destruction occurs by thermal conduction from the heated region. The total depth of necrosis depends upon the power level used and the length of time it is applied. The pattern of heating at the tip is hemispherical and monitoring the temperature of the adjacent tissue allows control over the depth of necrosis. A thermocouple on the applicator tip measures the temperature on the endometrial surface. There is a second thermocouple in the base of the applicator as a control and to show the temperature gradient. The temperature at the tip is displayed graphically allowing the surgeon to monitor the process of heating and hence treatment. The system computer screen provides the surgeon with a proven temperature band of 75 80°C. An alarm is activated if the temperature exceeds 85°C and automatically shuts off power at 90°C. Another safety feature is that potential perforation can be determined quickly by a failure to establish a temperature gradient if the machine is activated. No earthing is required and there is no energy transmission at the pre-set power levels beyond 6 mm from the applicator tip.

1.5 requirements for transcervical resection of the endometrium and microwave endometrial ablation

The main indication for endometrial destructive surgery is heavy menstrual blood loss in a women who has completed her family in whom surgical treatment is

indicated, but amenorrhoea is not a priority. Excessive uterine size, the presence of acute pelvic infection and evidence of pre-malignant or malignant disease are regarded as absolute contraindications(122). Ideally the uterus should be of normal size and should not have a cavity length of more than 12 cms(121). Small benign intrauterine lesions are not a contraindication to these techniques.

Transcervical resection of the endometrium

1.5a1 - Equipment

Transcervical resection of the endometrium is modelled on transurethral resection of the prostate and equipment requirements are similar. A 26 gauge modified urological resectoscope fitted with a fore-oblique lens of up to 30° is necessary which has separate inflow and outflow channels allowing continuous irrigation. Resection loops used in this centre are 7mm wide and 3mm deep and rollerballs are 4mm diameter cylinder / barrel type. A cold light source of 150 - 300 watts with flexible light cable is required for adequate visualisation alongside a modern camera system. A high frequency diathermy machine with variable waveform settings to enable supply of cutting, coagulative and blended currents as required, is also essential. A fluid distending medium is necessary to give a clear view of the uterine cavity when operating, it also has to be non-ionic to allow use of electrocautery. 1.5% glycine is the most commonly used irrigating fluid, as it has good optical qualities, is poorly miscible with blood and is not caramelised by electrocautery. It has the disadvantage of being a hypotonic solution and significant absorption can lead to hyponatraemia, hyperammonaemia and fluid overload which can lead to pulmonary and cerebral oedema, convulsions and death ("TURP syndrome"). It is important that input and output totals are measured and

the operation stopped once a deficit of 1500mls is reached. It has been shown that electrolyte disturbances does not occur at fluid deficits less than this(123). The deficit can be calculated by subtracting the amount collected from that infused, this is made easier by the use of a spring balance on the fluid bag(124). More accurate deficit calculation can be achieved by labelling the irrigating fluid with ethanol and measuring its concentration in expired respiratory gases(125). In order to distend the uterine walls, a pressure of 40 - 50 mm Hg is required. This is equivalent of gravitational pressure when a bag of fluid held one metre above the patients supine body(122), so peristaltic pumps or hysteromats are not strictly necessary. Hysteromats have a built in pressure limiting facility which may reduce the risk of sudden intravasation of irrigating fluid, and have been shown to reduce the fluid deficit by up to 85%(126). Outflow can be achieved through gravity, suction, peristaltic pumps or a combination of these.

1.5a2 - Preparation

All endometrial surgical techniques aim to destroy or remove 3 mm of myometrium so that endometrial glands are destroyed(120). In order to increase the chances of destroying these myometrial glands, endometrial thinning has been proposed to enhance the view and reduce the total amount of tissue that is required to be removed. Thin endometrium is present in the early proliferative stage of the menstrual cycle, but the practicalities of modern operating make it difficult to schedule operations by menstrual cycle. Although some surgeons undertake transcervical resection of the endometrium without endometrial thinning(127), the majority advocate the use of thinning agents for safer and more effective surgery(121,122). Endometrial atrophy can be induced using high dose

progestogens, danazol or gonadotrophin releasing hormone (GnRH) analogues. Progestogens cause patchy, unreliable atrophy leading to poor views(128) and are not used often now. Danazol and GnRH analogues both result in a predictable thin endometrium and their effectiveness has been shown in randomised controlled trials(129,130) and a large audit series(118). Both drugs also result in decreased fluid absorption, reduced operating times and improved menstrual outcomes(129). Danazol, although cheaper than GnRH analogues, has unpleasant side effects in the doses of 600 - 800mg/day for 4 - 6 weeks required, and hence compliance is a problem. The GnRH analogue, goserelin can be given subcutaneously and the effects last for 6 weeks(106), therefore compliance is not a problem. Goserelin 3.6mg can cause menopausal symptoms and has been shown to increase cervical resistance which is not reversed by prostaglandin administration pre-operatively(131).

1.5a3 - Technique

The majority of transcervical resection of the endometrium procedures are performed under general anaesthesia, although local anaesthesia can be used(96,132). The resectoscope is assembled and the light source, camera system and diathermy are connected. The cervix requires dilatation to 9mm before the resectoscope is introduced into the uterine cavity and irrigating fluid is started. Correct siting within the cavity is confirmed by identification of the tubal ostia before commencing treatment. Rollerball ablation of the fundus and cornual regions is undertaken followed by radial resection of the walls with a 90° loop. The resulting chippings of tissue are sent for pathological examination. Once completed the cavity is inspected and any troublesome bleeders or areas missed can be treated

with the rollerball. If bleeding persists an intrauterine foley catheter can tamponade the uterine cavity for 6 - 12 hours and invariably results in haemostasis. Broad spectrum antibiotic cover is recommended(102,103), and has been shown to significantly reduce peri-operative bacteraemia(133).

Microwave

1.5b1 - Equipment

The microwave generator, magnetron, (Microsulis PLC, UK) is housed in a protective casing which also contains a computer for data storage and a keyboard to initiate commands and input data. A computer screen allows patient information to be viewed and, in treatment mode, a visual display of temperature against time is shown with a band from 75-80°C, which represents optimal operating temperature. Two flexible cables, one transmitting microwave energy the other for data collection are connected from the operating probe to the generator. The hand held operating probe is 8mm in diameter and is 15 cms long, graded in centimetres. Microwaves generated at 9.2 GHz are transmitted to the tip of the probe when the footpedal is activated. At 30 W, energies of 1.5 - 9.3 kJ result. A ball of microwave energy is created at the probe tip, which at the predetermined energy setting, ensures depth of tissue penetration to a maximum of 6 mm. Thermocouples are present at the base and tip of the operative probe allowing accurate measurement of the temperature gradient, which is displayed on the screen.

1.5b2 - Preparation

As depth of tissue penetration is constant, at < 6mms, with the microwave, a thick endometrium may result in failure to destroy deeper endometrial glandular tissue.

For this reason endometrial thinning agents are required for all patients undergoing this ablative technique. These are as previously described in 1.5a2

1.5b3 - Technique

The procedure is generally performed under general anaesthesia, although local anaesthetic can be used(134). The cervix is dilated to 9mms and the length of the cavity measured. The probe is inserted until the tip reaches the fundus, ensuring that the length inserted is the same as that previously measured. The microwave generator is then activated by depressing the footswitch. Once the tissue temperature reaches 75-80°C the probe is moved laterally into the cornual region. The temperature reading will transiently fall, then once the operating temperature is attained again the probe is moved to the opposite cornua and the process repeated. The probe is then gradually withdrawn whilst maintaining the temperature in the 75-80°C range. The technique effectively "paints" the uterine cavity with a broad brush of destructive microwave energy(114). The treatment phase should be stopped once a coloured area appears on the probe shaft. This is set 3cms from the tip and ensures that the endocervical canal is not treated which could result in stenosis with subsequent haematometria or pain. The treatment time varies with cavity length, but is usually between 2 - 3 minutes.

1.6 The place of endometrial surgery in the management of heavy menstrual loss - a critical review of the literature

Endometrial resection was initially used to treat intractable uterine bleeding in women who were unfit for hysterectomy because of blood dyscrasias or extreme anaesthetic risk(95). Follow-up of these women revealed high amenorrhoea rates.

Endometrial ablative surgical techniques were then proposed as alternatives to hysterectomy for healthy women and were advocated for use after medical treatment had failed(96,121,135,136). The enthusiasm of surgeons and patients alike resulted in the development and promotion of endometrial resection techniques without randomised controlled trials(137). The expected fall in hysterectomy rates has not yet materialised, despite a substantial increase in the number of ablative procedures undertaken(51,60,138), although there is evidence of regional exceptions to this trend(139). In 1991, 56% of NHS gynaecological units in the UK were offering one of these ablative techniques, by 1993 this had risen to 83%(140). There is a concern that the threshold for surgical intervention has fallen with the introduction of these procedures, although alternatively, women who would never previously considered having a hysterectomy could be presenting for treatment now that a less invasive surgical solution is available(56,91). Despite not replacing hysterectomy for dysfunctional uterine bleeding, these techniques have become very popular with clinicians and it would seem, with women themselves.

Endometrial ablation has reached the fourth and final phase of validation. The indications for its use are now clear as are the advantages and disadvantages of the procedure(136). This statement was based on the progression from innovation of these new techniques in the 1980's, through reports of personal series to finally, in the 1990's, the completion of a number of randomised controlled trials. Five randomised controlled trials(104-108) have compared hysteroscopic surgery with hysterectomy, one has compared ELA with TCRE(109), and another, TCRE with a progestogen loaded IUCD(83). These, in conjunction with two large national audits have confirmed the safety and effectiveness of these hysteroscopic surgical

techniques(59,118). Few surgical techniques have been so rigorously evaluated and yet its true place in the management of women with excessive menstrual loss remains to be fully established.

In the early 1990's a large prospective series of endoscopic laser ablation(102) reported satisfaction rates of 97%, amenorrhoea rates of 60%, a hysterectomy rate of 3% after six month and no major complications. Similar results were presented at the same time for 250 transcervical resection of the endometrium operations(103) over follow up times of up to 2.5 years. Advocates of rollerball ablation had presented equally high satisfaction rates with low complications for their patients, but in smaller series of women(97,98). Although these results were encouraging and seemed to suggest that these techniques were safe and effective, these reports were subject to a number of obvious biases. The operations were undertaken by enthusiastic proponents of these procedures, whilst it is also likely that only highly motivated patients were recruited. No baseline data are available to estimate the patients degree of dysfunction, hence making outcome data difficult to interpret. No comparative controls are present and if there were, could not be matched for all prognostic and confounding variables. Nothing is known of how many women were lost to follow up, the number of eligible women who had the operation, or indeed what proportion of those operated on completed questionnaires. Observational studies of this type are subject to many problems the most serious of which is selection bias(141). This can lead to over optimistic claims being made about the intervention under investigation(142). The only way to convince the medical and scientific world of the merits of hysteroscopic surgery was to

undertake randomised controlled trials and this was acknowledged by proponents of these techniques(143).

1.6a - Hysteroscopic endometrial surgery versus hysterectomy

The obvious reference for comparison for these procedures was the hysterectomy. This was based on the possibility of reducing the number of hysterectomies undertaken, at least 50% of which are for excessive menstrual loss(51). One obvious drawback, was that hysterectomy guaranteed amenorrhoea, whereas even the most optimistic reports gave amenorrhoea rates of only 60% for endometrial ablation. Morbidity, recovery times and economic evaluations of each procedure were tangible end points that could be measured. Other, more global criteria for treatment outcome were required which were tangible to the patient, such as satisfaction with, and acceptability of procedures, improvements in quality of life and changes in psychological and sexual functioning. Unfortunately, suitable measurement tools, and more importantly, normative reference values had not been established for most of these outcome parameters when many of these trials were commenced.

The first randomised controlled trial evaluating endometrial ablation, from 1991, compared transcervical resection of the endometrium with hysterectomy(104). 51 of 54 randomised women received their allocated treatment (26/28 had hysterectomy, 25/26 had TCRE), operating time, post-operative recovery, morbidity and costs of surgery (£400 v £1270), all favoured transcervical resection of the endometrium. Despite critical flaws of small numbers, no a priori hypothesis or a power study based on it, and the bias that women were recruited from a waiting list for

hysterectomy; the results were similar to and supported the reports from the published observational data.

The next randomised controlled trial was published in 1991(105). This was methodologically more robust, with a power study calculated on the basis of differences in patient satisfaction, and clear and sensible entry criteria were made. 100 women were required in each arm, however, after withdrawals, 97 underwent hysterectomy and 99 TCRE, and at four month only two women, from the hysterectomy arm were lost to follow-up. The only recognised and validated assessment tool used was the general health questionnaire (GHQ)(144). All operative data significantly favoured TCRE, including operating times, post operative pain and complications, and recovery time. Three (4%) of those undergoing TCRE suffered blunt uterine perforation. Those women very satisfied were significantly more likely to have had hysterectomy (94% v 85%), although 95% in each arm were satisfied and would recommend their operation. Premenstrual symptoms were significantly reduced by both techniques, but significantly more so by hysterectomy for most symptoms. Dysmenorrhoea was absent in 94% of women following hysterectomy, but only 62% of women with TCRE (15% of women at baseline had no dysmenorrhoea). Four of the six women who were dissatisfied with their hysterectomy, had baseline GHQ scores greater than 12, indicating psychiatric morbidity. After four months, 11% of women in the TCRE arm had requested further surgery, 4% having a hysterectomy. An amenorrhoea rate of only 16% was obtained for TCRE which was much lower than previously reported. It must be noted that pre-operative endometrial thinning was not administered in this study. An economic evaluation of health service costs of each procedure was also

undertaken at four months(145) which showed TCRE to be significantly less costly than hysterectomy (£513 v £1230).

These women were followed up by postal questionnaire again at an average of 2.8 years later and a repeat economic evaluation was also undertaken(55). A 79% response rate was obtained, 155/196 women, which is only 75% of the requirements for the power study. By now tools for measuring health related quality of life were available which were validated for the UK population. Two of these, SF-36(146) and EuroQol(147) were utilised. Marginally, but not significantly better scores were achieved for the hysterectomy group for both quality of life questionnaires, but both groups scores for SF-36 were comparable to normative data for the healthy female population aged 35 - 50 years(148). Unfortunately the most important outcome, change in scores from baseline could not be determined. Women remained significantly more satisfied in the hysterectomy group (93% v 79%), and a significant change occurred in those who would recommend their allocated operation (75% TCRE v 96% hysterectomy). Pain, premenstrual symptoms and workdays lost were all significantly less in the hysterectomy arm by this stage. The retreatment rates had risen from 11% at four months to 23% at 2.8 years, with a 16% hysterectomy rate. Excluding those who had undergone hysterectomy, the amenorrhoea rate in the TCRE group was only 13%. Health services costs, still favoured TCRE, although the gap had narrowed between the two procedures (£790 v £1110).

The next randomised controlled trial, conservative alternatives to hysterectomy (CATH 1), was published in 1994(106). It was similar to the Bristol trial in terms of

power study numbers, again based on patient satisfaction. Important differences were that endometrial thinning was undertaken in the ablation arm using goserelin 3.6mg five weeks pre-operatively, TCRE and ELA were allocated equally amongst those randomised to ablation, and five different surgeons undertook the ablative procedures. Health related quality of life was not assessed although psychiatric and psychosocial parameters were measured. No significant differences were detected between TCRE and ELA, and so were combined and compared to hysterectomy, of which 90% were abdominal procedures. Operative results again favoured the ablation arm, with significantly shorter operating times, less post operative morbidity and shorter hospitalisation and time to recovery. At twelve months satisfaction rates were significantly better after hysterectomy (89% v 78%). Dysmenorrhoea and premenstrual symptoms were both greatly reduced by all operations at one year, with no significant difference between ablation and hysterectomy. Psychometric parameters were assessed and presented in a complimentary paper(149). Both treatments reduced anxiety and depression scores and there were no differences in mental health or sexual function between the two at twelve months. Personality and duration of menstrual dysfunction had no influence on outcome. 10% had undergone repeat TCRE and 16% hysterectomy. A third paper assessing the economic issues of this trial concluded that the NHS costs of ablative surgery were significantly less than hysterectomy by 20 - 24% (£1001 - TCRE; £1024 - ELA; v £1315, hysterectomy)(150). On average women undergoing the hysteroscopic procedures incurred 71% less costs to themselves than those undergoing hysterectomy (£21 v £73.40).

Four year follow-up data are now available for the clinical and economic outcomes(151). The risk of having any further surgery if initially allocated to TCRE was 36%, and by hysterectomy was 24%. Satisfaction remained high in both arms, 80% for TCRE and 89% for hysterectomy, remembering that analysis was by intention to treat. Premenstrual symptoms and pain remain significantly better than at baseline, the effect size being greater with hysterectomy. Psychosocial parameters remain significantly improved from baseline and equivalent between groups, but no different from one year results. The economic differences between the two procedures had narrowed from the one year figures with ablation being 93% of the cost of hysterectomy (£1231, TCRE/ELA; v £1332, hysterectomy). As women recruited to this trial were initially referred for hysterectomy, 76% have avoided it at four years.

The fourth trial to be published was the Medical Research Council (MRC) funded randomised trial of endometrial resection versus hysterectomy(107). This although having an a priori hypothesis and power study based on it turned into an inadequate study from a methodological point of view. It gains credibility by virtue of the similarity of its results to the Bristol and Aberdeen randomised controlled trials. Its strong points were sensible entry criteria, potentially increased generalisability as teaching centres and district general hospitals participated, and half of the hysterectomies were vaginal. The power study calculation determined 202 patients required at three years, however subsequent randomisation was unequal, 2:1 in favour of TCRE, and the power study was not adjusted for this. The power study numbers were achieved by the end of recruitment phase with 68 in the hysterectomy arm and 134 in the TCRE arm, but no extra were recruited to

compensate for inevitable drop-out. By three years data were available for only 28/68 and 54/134 respectively, well below the required numbers. Another major problem affecting external validity of the results was that only 25% of eligible women participated. Women not recruited invariably had a strong treatment preference. This could have been predicted had a pilot study been undertaken. Essentially the results concurred with those previously published, but because of the methodological flaws, the results are difficult to interpret in their own right. Re-operation rates were 22% in the TCRE arm and 9% in the hysterectomy arm at three years.

The final randomised controlled trial compared TCRE with vaginal hysterectomy(108), suffered from similar power study flaws as the MRC trial above. A power study was calculated on the basis of a difference in means, but for a subjective variable, in which one arm the outcome was known to be 0 with 0 standard deviation. (pictorial assessment of menstrual blood loss). This was then not used as the principal outcome measure, but the power study calculation kept. Statements of no difference in satisfaction rates, (95% hysterectomy v 87% TCRE) and sexual functioning scores cannot be made from the 77 women in whom results were obtained at two years. Health related quality of life was measured at two years by SF-36 and hysterectomy was better for all parameters and equivalent to Italian normative values. Unfortunately, baseline SF-36 scores were not obtained and so change scores were not available.

Two national audits have been undertaken in Scotland(118), and in England(59). The Scottish audit, took place over two years between December 1991 and

December 1993, relatively early in the introduction of hysteroscopic surgery into gynaecological practice in the country. 978 cases were registered of which 732 women were followed up at six months, 554 at twelve and 80 at 24 months. The numbers were too small to confidently estimate procedure mortality or life threatening complications but were encouraging. Complications occurred in 12% of cases including one death from toxic shock syndrome(152). Uterine perforation and significant fluid overload occurred in 1%. At twelve months satisfaction rates were 84% whilst repeat procedures had been undertaken in 13% and hysterectomy in 11%. At two years there was a 17% repeat ablation and 15% hysterectomy rate. There was no statistical evidence of an association between occurrence of complications and operator experience. The majority of procedures were TCRE's (65%), ELA's contributed 32%, the rest were rollerball ablations.

The results of the RCOG Clinical Audit Group (MISTLETOE survey)(59) reported on 10 686 procedures undertaken over 18 months from April 1993. This survey had sufficient numbers to assess mortality, and crude differences between the different hysteroscopic techniques. Two deaths were directly attributable to the procedures, immediate complication rates ranged from 2.6% (ELA) - 6.4% (loop resection). Combined rollerball / loop resection was the most widely practised technique, and had immediate complication rates of 4.6%. TCRE by any method accounted for 75% of all endometrial destructive procedures. These results certainly confirm that these procedures have a low morbidity and mortality. The statements made with regards to ELA being the safest procedure with total loop resection the least safe, although evident from the data surveyed must be regarded with caution. It is more likely that expensive laser systems are in tertiary teaching centres and with the

prerequisite safety requirements, surgeons are more likely to have been trained in its use. Equipment for TCRE is cheap and readily available, and at the time of the survey there were no necessary training requirements for its use. It is possible that these factors may have contributed to the differences, as in the only randomised controlled trial comparing ELA with TCRE techniques these differences were not detected(109).

Overall the results of these randomised controlled trials and national audits generally support the results and claims of the previously published observational studies, though with slightly more cautious enthusiasm and with the acknowledgement that long term results, not only in terms of outcome, but of unsuspected co-morbidity must be awaited. They also confirm that hysterectomy is an effective treatment for heavy menstrual loss. Despite methodological shortcomings in some of the trials, the results are remarkably consistent. Operating times, complications hospital stay and recovery times are significantly less than for hysterectomy. Satisfaction rates are maintained at around 80% at four years and dysmenorrhoea is significantly reduced. Re-operation rates average out at about 16% at one year, rising to 22% at two to three, and reaching 34% at four to five years. Accepting that these were all women who would otherwise have had a hysterectomy, then at four years 76% of women who fulfil the trial criteria, could have avoided a major operation. The worsening menstrual flow and increasing pain rates in these trials were in keeping with a previous series report(153). What is not known yet is the effect on subsequent endometrial malignancy rates, presentation and behaviour. A number of carcinomas have been detected from resection loop specimens despite pre-surgery negative endometrial biopsy(154,155)

and there are reports of late presentation of carcinoma arising following TCRE's with negative chippings(156).

Prognostic variables which influence success rates for these procedures have been identified from large series reports as well as randomised controlled trials. It seems that women with true menorrhagia, menstrual blood loss of >80 mls/cycle, have a better outcome than those whose menstrual loss is less than this(157). Women over the age of 35 - 40 years do better than those younger than this(103,158). Superficial adenomyosis can be treated definitively with endometrial ablation, but deep adenomyosis responds poorly(159), however the ability to differentiate between varying extents of adenomyosis cannot be made at ablation and adenomyotic changes may in fact represent thermal artefact on resection chips. Polyps or small submucous fibroids are not contraindications to treatment(160). Dysmenorrhoea and premenstrual syndrome symptoms diminish following ablative procedures(106,109), the reduction in PMS symptoms correlates with the reduction in menstrual blood loss(161). For uterii clinically under ten weeks size, 95% of TCRE or ELA operations were completed without prior diagnostic hysteroscopy(106), suggesting that this investigation is only routinely indicated if the uterine size cannot be assessed or feels enlarged. Overall the best results can be expected in women over the age of 45 who have proven menorrhagia due to dysfunctional bleeding, which is unresponsive to drug treatment, and who are otherwise faced with hysterectomy. There is no difference in outcome for women with regular or irregular periods(162). Women without a preference and who do not expect amenorrhoea will also have a lower failure rate(163).

1.6b - Hysteroscopic endometrial surgery versus other modalities

Three published randomised controlled trials exist comparing ablative techniques with a treatment other than hysterectomy. One compares two hysteroscopic surgical techniques, TCRE and ELA(109); the second compares TCRE with the levonorgestrel intrauterine device(83) whilst the third compares rollerball ablation with the uterine thermal balloon(164).

The randomised trial comparing TCRE with ELA continued recruitment from a previous trial comparing endometrial surgery with hysterectomy which did not have sufficient power to detect differences between the two hysteroscopic techniques. This was an a priori decision, and women were randomised to either ELA or TCRE in the original trial. A further 167 women were subsequently randomised, making 382 in total, exceeding the 350 required for the power study. Satisfaction rates after one year were high and equivalent at 90%. TCRE was significantly quicker, resulted in less fluid absorption, and was cheaper. Re-operation rates were lower for TCRE (16% v 20%), but this was not significant. Morbidity rates were low for both techniques. These results are at one year follow-up and may alter with time. The second phase of randomisation undertaken to fulfil the power requirements will almost certainly have recruited different women from the first phase, although as equal randomisation took place this should not have affected the results. The first 105 women randomised had been referred for surgical treatment when hysterectomy was the option, whereas in the second phase women were recruited who were not expecting or offered hysterectomy as an option. These results have been upheld by the national audits(59,118), although the largest of these found that ELA was the less morbid procedure.

The most promising non-surgical advance in the management of excessive menstrual loss is the levonorgestrel intrauterine device, which has only recently gained a license in the UK for this use despite evidence of its efficacy. Reductions in menstrual loss of over 90% have been achieved in series reports(81,165). Similar results were achieved in a randomised controlled trial comparing it with oral progestogens for women with objectively proven menorrhagia(80). A further study showed its ability to significantly reduce the hysterectomy rate of women on the waiting list for hysterectomy who were randomised to have the Mirena intrauterine system or not(82). There were limitations to this trial, the most obvious being the initially biased waiting list population (nothing to lose), no power study, and a high (14%) number of women in the control arm who did not have a hysterectomy anyway. The corrected number avoiding hysterectomy was therefore 50%.

The only randomised controlled trial comparing levonorgestrel with endometrial ablation again was methodologically flawed. Crosignani et al(83) randomised 70 women, aged 38 or more, who were referred for hysterectomy, to TCRE or the levonorgestrel intrauterine device. The power study was based on detecting a 30 ml difference in observed menstrual blood loss, using a difference in means, although subjective, pictorial charts were used and the standard deviation estimated. This allowed them to fulfil the power study requirements easily as only thirty women were required in each arm. These numbers are far too small to detect differences in important subjective parameters such as satisfaction and quality of life which were nevertheless still measured and commented on. After one year side effects were higher in the levonorgestrol arm, but satisfaction rates of 85% were achieved compared to 90% for TCRE. Pictorial blood loss assessment revealed a 79%

reduction for the intrauterine device, significantly less than the 89% achieved for TCRE. The distribution of SF-36 scores were equivalent for both methods of treatment, baseline scores were not measured and so changes in scores were not ascertained. There is mounting evidence that the levonorgestrel intrauterine device has many potential advantages, the avoidance of an operation, reversible effective contraception and appears to be effective in reducing menstrual blood loss. In this trial it did not perform as well as TCRE although better designed randomised controlled trials are required comparing this treatment with the best of the ablative techniques in the future.

The thermal balloon was compared to rollerball ablation in America in a multicentre randomised trial with adequate numbers(164). Unfortunately, neither technique has been previously evaluated in the context of a randomised controlled trial, and so two new techniques were being compared without an established "benchmark" control group. Secondly, the entry criteria determined that only women with regular endometrial cavities of up to 8 cms could be included. This significantly limits the generalisability of the results when all women referred with heavy menstrual loss are considered. The results from the trial are however encouraging. Satisfaction rates were equivalent and similar to previous trial results, with a marked improvement in quality of life parameters and highly significant and equal reduction in menstrual loss. The only difference was that the thermal balloon was significantly faster and possibly safer, although numbers were too small to detect a significant difference.

There is no doubt that endometrial surgical techniques have been subjected to more rigorous evaluation than almost any other surgical procedure and all in a timescale of under ten years. Despite methodological shortcomings in some of the trials, the overall results are consistent and encouraging. Two areas of research remain deficient however; establishing the place of these techniques in the management of women with excessive menstruation, and a comparison of the most promising new ablative techniques with a proven hysteroscopic technique. This thesis will present results from two randomised trials which attempt to correct these deficiencies. The first randomised controlled trial compares traditional medical therapy with TCRE, the second compares microwave endometrial ablation with TCRE.

Table 1.1:- Summary of randomised controlled trials evaluating transcervical resection of the endometrium

Study	Comparison	Number of patients (TCRE+other)	Follow -up time	Procedure time (mins)	Complications	Satisfaction (%)	TCRE - Hypo / amenorrhoea %
1. Gannon, et al(104) 1991	abdominal hysterectomy	51 (26 + 25)	9 - 16 months	30 - TCRE 50 - TAH	0% TCRE 46% TAH	84% TCRE	80% TCRE (64% amen.)
2a. Dwyer, et al(105), 1993	abdominal hysterectomy	196 (97+ 99)	4 months	35 - TCRE 45 - TAH	4% TCRE 47% TAH	85% TCRE 94% TAH	89% TCRE (13% amen.)
2b. Sculpher, et al(55) 1996			24 months			77% TCRE 96% TAH	70% TCRE (13% amen
3. Pinion, et al(106), 1994	hysterectomy	204 (105 + 99)	12 months	45- ablation 61 - hyst	1% ablation 5% hyst.	78% ablation 89% hyst	76% ablation (22% amen.)
4. O'Connor, et al(107), 1997	hysterectomy	172 (116 + 56)	up to 4 years	32 - TCRE 66 - hyst	13% TCRE 45% TAH	85% TCRE 96% hyst	TCRE, 21% amen. at 21 months
5. Crosignani et al(108), 1997	vaginal hysterectomy	85 (41 + 44)	2 years	13- ablation 71 - hyst	0% ablation 2% hyst	87% ablation 95% hyst	64% ablation (22% amen.)
6. Bhattacharya, et al(109), 1997	endometrial laser ablation	372 (188 = 184	2 years	21 - TCRE 30 - laser	10% TCRE 14% laser	91% TCRE 90% laser	86% TCRE 85% laser
7. Crosignani et al(83), 1997	levonorgesterol IUCD	70 (35 + 35)	12 months	not given	none	95% TCRE 85% IUCD	75% TCRE 65% IUCD

Chapter 2

Epidemiology, Demography and Preferences of Women Referred for Management of Heavy Menstrual Loss.

(patterns of referral, socio-demographic details, history and perceived severity of presenting complaint, primary care treatment, effect on health related quality of life, and expectations of treatment).

It is well known that rates of hysterectomy vary widely at international level(166), although there is conflicting evidence when rates between different health authorities in Britain are compared(61,167). General practice referral rates for menstrual problems also show wide regional variations(168), as do drug prescribing patterns for menorrhagia(169). These variations may reflect differing expectations of treatment, perception of severity of complaint, doctor and patient preferences, but most likely represent an interplay of all these factors.

There is a paucity of national data regarding patterns of referral for treatment, treatment preferences, expectations of treatment and socio-demographic features of women with heavy menstrual loss. What little there is has centred on a population in one regional health authority of England, Oxford, and concentrates principally on primary care(49,62,63,169). One study demonstrated that 43% of women with menorrhagia were referred to a gynaecologist within a month of seeing their general practitioner and that 45% had not been prescribed medical treatment(49). 36% of women referred to the gynaecologist had a treatment preference and the strongest predictors for having a preference were higher education and previous consultation with gynaecological problems(63). Many experts have argued that patient preference should be an important guide to treatment choice, and may strongly influence outcome success(23,35).

Traditionally, menorrhagia has been a diagnosis based on measured menstrual blood loss above 80mls per cycle(48), and 67% of women losing more than this

show evidence of anaemia. On an average Western diet a blood loss of over 60mls per cycle will result in a negative iron balance(35). These measurements are not very helpful in everyday management of women complaining of excessive menstrual loss as their symptoms and complaints are not usually related to anaemia. Indeed the majority of women complaining of heavy menstrual loss do not have true menorrhagia(30-32,48). What is more important to the majority of women is the effect of their menstrual loss on their everyday function, or health related quality of life. Baseline "normative" values of health related quality of life, using the generic health questionnaire, SF-36(146,170) have been obtained for the general population(148). It has been demonstrated that for women with heavy menstrual loss in primary care in Grampian, that seven of the eight dimensions of SF-36 were significantly reduced(53). It has also been shown, in a prospective observational study, that women treated surgically had greater improvements in their quality of life scales than those without treatment or those treated medically(171). What has not been demonstrated is whether women with a particular treatment preference have different quality of life scores at baseline, which may influence choice of management, or the degree of improvement in quality of life they can expect to gain.

There is evidence that consultation rates for menstrual complaints are on the increase (Royal College of General Practitioners 1994). In order that this extra work is not automatically accepted and transferred to specialist clinics, epidemiological work is needed to detect any recognisable patterns or reasons for its occurrence. This requires baseline questioning of women referred with menstrual problems and establishing a programme of guidelines for menstrual management in primary care

and education programmes / information packages for patients. Ideally this should be a national undertaking, but determining local values is important because of regional variation between populations. Once this is established, an audit cycle can be initiated to ascertain the impact of such guidelines on primary care, for example as compiled by the Royal College of Obstetricians and Gynaecologists(65), on changes in referral and treatment rates.

The population study described in the following chapter outlines the socio-demographic background, clinical status and levels of health related quality of life of women referred for the first time to the gynaecology clinic in Aberdeen with heavy menstrual loss. It also seeks to determine the proportion of women who have treatment preferences and whether these women are different from those with no preference, who accepted randomisation to medical treatment or endometrial destructive surgery.

PATIENTS AND METHODS

Eligibility

From 1st October 1994 until 30th September 1995, all women with heavy menstrual loss who were first time attendees at the clinics of the nine participating gynaecologists at Aberdeen Royal Infirmary, were identified by screening referral letters. Women were excluded who had been previously seen at the hospital for heavy menstrual loss and those who had clinical evidence or concern of underlying pathology which excluded a diagnosis of d.u.b., or which necessitated hysterectomy.

Protocol

Following local research ethics committee approval, eligible women were all given a socio-demographic questionnaire, which also contained a clinical component (Appendix 2.1), Short form 36 (SF-36)(146), (Appendix 1a), and the hospital anxiety and depression scale (HADS)(172), (Appendix 1b). These questionnaires were self completed by the women at the gynaecology clinic. Non-directive assistance for questions that were not understood was available. Specifically, questions determined length of times with complaint, number of visits to the general practitioner with it, number of treatments received, their perception of the severity of their heavy menstrual loss, their treatment preference if this existed, and expectations of treatment. Level of education, employment and type of domicile were also determined, and finally effect of their complaint on health related quality of life. These women were the target population for the randomised trial comparing TCRE with medical treatment which is described in chapter 3. Women with treatment preferences and hence were not suitable for randomisation completed a short questionnaire to determine reasons for preference (Appendix 2.2).

Women who did not agree to randomisation to the trial of TCRE versus medical treatment were asked to give their reason for refusal. If this was because of a specific preference for one type of treatment, then this was established. After completing their questionnaires women were then allocated treatment according to their wishes, if appropriate, or as determined by randomisation. Those expressing a treatment preference were asked what factors influenced this.

Statistics

Data were entered onto a database created on SPSS for windows, and all analyses were undertaken using this programme or by InStat version 2 (GraphPad software). In general results are statements of prevalence and rates within the target population with means or medians stated where necessary. Where between group comparisons are made then categorical data were compared using the chi square test, continuous data with normal distribution were analysed using the Student t test or by analysis of variance (ANOVA), and if not normally distributed the Mann-Whitney U test was utilised.

RESULTS

Patient characteristics

273 women with excessive menstrual loss were referred for the first time to the gynaecology clinic of the nine participating gynaecologists over a twelve month period from 1st October 1994 until 30th September 1995. All 273 self completed the baseline socio-demographic and clinical questionnaires and the results are outlined in table 2.1. This reveals that the majority of women had previously consulted their general practitioner and received treatment from them prior to referral, but 21% had their menstrual problem for less than twelve months and 22% had never received any medical treatment prior to referral. A high proportion, 64% were disabled for more than two days per cycle. The baseline SF-36 scores (table 2.2 and figure 2.1), reveal a global and significant reduction for all eight components when compared with the normative values for the UK population(148).

Patient preference

A treatment preference was expressed by 31% of the target population. Compared to those without a preference, women who exhibited a treatment preference were significantly more likely to have less than two children and to have been previously treated by their general practitioners for heavy menstrual loss (table 2.3). Women with a preference had higher scores for seven of the eight SF-36 dimensions and also for the anxiety component of the HAD scale (table 2.2) although these differences did not reach the 5% significance level.

When the preference group were analysed separately, differences were evident between those who preferred surgery and those preferring medicine. Significantly more women with a preference for TCRE had previously received treatment for heavy periods, were more likely to hope for amenorrhoea, and were more likely to be disabled for more than two days per cycle by their period. They were also significantly less likely to own their own property whilst fewer had continued their education past the age of 16.

Those with a medical preference scored significantly better for all components of SF-36 except physical functioning and general health (table 2.1, figure 2.2). Their HAD scale depression scores were also significantly better than those with no preference or preferring TCRE, although all groups were within the normal range (table 2.2). The anxiety component of HADS was within the normal range (score < 8), for those preferring medical treatment, and higher than 8 for those preferring TCRE or with no preference, although there was no statistically significant difference between the groups (table 2.2, 2.4).

Health related quality of life

Health Related Quality of Life was measured in all participants at baseline using the generic health questionnaire, SF-36. At baseline, those women preferring medical treatment scored significantly better for six of the eight parameters, whereas those without a preference or preferring TCRE, which had similar mean scores that were significantly lower than mean normative values (table 2.2 and Figure 2.2). The mean scores for women in the preferred medical therapy group were, in fact, similar to mean normative values for British women of this age group for five of the eight variables(148), with little scope for improvement with treatment for the other three.

Reason for preference

The reasons given for having a treatment preference were also ascertained from these women. Both medical treatment and TCRE had been recommended equally often by the patients' general practitioners. No patients had been "recommended" medical treatment by friends or through the media, whereas 52% of those choosing TCRE had. The majority (84%) of patients choosing TCRE would not consider medical treatment at all whereas all those choosing medical treatment would consider having a TCRE later. The most important consideration for those choosing medical treatment was the desire to avoid having an anaesthetic or surgery if possible, whereas the most important reason for choosing to have a TCRE was the desire to avoid long term medication.

DISCUSSION

This represents the first assessment of the socio-demographic, clinical and quality of life status of women referred to a gynaecologist for the first time with excessive menstrual loss. 273 women who fulfilled the criteria attended the gynaecology clinic representing 7.3% of all new general gynaecological referrals to the nine participating gynaecologists in Aberdeen. If re-referrals to gynaecology clinics with excessive menstrual loss(48) are included then proportion rises to 8.3%. This figure does not take into account referrals to peripheral clinics in Grampian or private referrals. The two non-participating gynaecologists should not alter the figures as the general referrals are equally distributed amongst the eleven consultants. The proportion of women with heavy menses will be slightly underestimated as the total number of referrals incorporates some women referred to specialist psychosexual and menopause clinics. Even so the total is less than the 12% quoted by Bradlow and colleagues for Oxford(47), which may represent a combination of variations in thresholds for referral, patient expectations and tolerance of symptoms.

Few women under thirty or without children were referred for treatment and the majority (89%), had consulted their general practitioner on a previous occasion regarding excessive menstrual loss. It is perhaps disappointing to note that 21% had their complaint for less than one year and a similar number had received no treatment from their own doctor prior to referral. These are better figures than obtained from primary care in Oxford region where 45% were referred without treatment and 43% within one month of consulting their general practitioner(49).

These regional variations may represent a reluctance to treat menstrual problems in primary care, perceived or real patient pressure for referral, or the knowledge of longer waiting times for specialist treatment in different parts of the UK. Caution must be used when using Oxford data as the British reference as although it is the only presently available comparison it is highly unlikely to be representative of the whole of the country. There is little doubt that the differences in previous treatments received, number of consultations, and time from consultation to referral reflect wide variations in primary care management. If the Royal College primary care guidelines(65) had been available, and instituted at the time of this study then approximately 20% of the women were inappropriately referred.

Each year in the UK £7 million is spent on prescriptions in primary care to treat menorrhagia(65), this is despite the fact that between 22% and 45% have received no treatment prior to specialist referral. A high proportion of women (64%) are disabled for more than two days per cycle, despite the aforementioned treatment rates in primary care. A previous study revealed that only 12% of women with menorrhagia are maintained on drug therapy after five years and 60% will have had a hysterectomy(49). These figures were obtained between 1984 and 1989, before the introduction of endometrial ablative surgery and the progestogen intrauterine device in the UK. These statistics have enormous resource implications through work days lost and possibly ineffective prescribing, making the initiation of effective and acceptable treatment at primary care level a priority.

Traditionally, assessment of heavy menstrual loss and treatment with medical managements has been based on objective menstrual blood loss and its effect on

haemoglobin levels or iron stores. This is of little relevance to the vast majority of women who seek help for their troublesome bleeding. Totally subjective assessment of menstrual blood loss, particularly retrospectively is notoriously unreliable. Semi-quantative, prospectively completed, pictorial menstrual charts have been devised which have been shown to be high levels of sensitivity and specificity(34,157). These may have been useful additions to this and other studies involving women with menstrual problems as the results are amenable to statistical analysis making inter and between group comparison more reliable. Secondly in this study it would enabled determination of the prevailing level of true menorrhagia (loss >80 mls/cycle). More recently, measurements of health related quality of life issues have been recognised as important determinants, not only of level of suffering, but also as measures of response to treatment(51). Health related quality of life can be effectively measured using a number of tools, although the generic health questionnaire SF-36 has been shown to be sensitive in detecting changes in quality of life for specific medical conditions, including menorrhagia(52,53,171,173). Women have been shown to benefit from a greater improvement in quality of life parameters following hysterectomy than after non-surgical treatment of menorrhagia(54). Normative values for SF-36 are available for the healthy population, of different age groups, and both sexes(148). Ideally normative data at a regional level would be available, although comparing a woman's score with these national values allows an assessment of her heavy periods for the different health dimensions measured, and can predict how effective certain treatments might be in improving these.

This study reveals that women referred for the first time to a gynaecologist with heavy menstrual loss have a global and significant reduction in all eight dimensions of quality of life as measured by SF-36. This demonstrates that these women are deserving of treatments to try to return these levels towards normality. Advocates of measuring menstrual blood loss and treating only those who lose more than 80 mls per cycle would not treat the majority of women, yet have not demonstrated that reassurance alone for those with normal blood loss will improve their quality of life. Importantly this study also reveals that differences in quality of life scores vary according to treatment preference. Women with a strong preference for medical treatment have SF-36 scores that are near normal and have little scope for improvement irrespective of type of treatment. It would be sensible to concur with their wishes, or if necessary demonstrate that no treatment is required so that interventions with increased morbidity, which may not afford them tangible benefit, are avoided. Those with a surgical, or no preference were equally debilitated by their heavy periods with respect to quality of life.

Patient preference is regarded by some experts as an important arbiter of treatment choice in menorrhagia(23,35). There is a paucity of information in the literature describing rates of preference, on differences in baseline characteristics of those exhibiting a preference, and of the expectations of these women. Our rate of expressed preference (31%) is lower than the rate of 36% described by Coulter and colleagues in a large primary care based observational study of women attending their general practitioner with heavy menstrual loss(63). Treatment preference was identified as the principle reason for refusal of randomisation when medical and surgical management were compared in a randomised trial involving termination

of pregnancy(174). Outcomes with regards to patient satisfaction and acceptability also varied on the basis of preference. This study highlighted the importance that patient preference can have on determining outcome and generalisability of trials. The importance and effect of patient preference was made evident by the randomisation rate of only 25% achieved in the MRC trial of TCRE versus hysterectomy because of strong patient opinions regarding their treatment(107). This prolonged recruitment and decreased generalisability could have been predicted if piloting had been undertaken to identify the very high preference rates for these treatments in that region.

There were systematic differences between the preference groups and those who expressed no treatment preference. Women who preferred medical management tended to have better general health, were less restricted by their menstrual problems, and fewer had been treated previously by their GP. On the basis of their SF-36 scores they were not as severely affected by their periods, with near normal quality of life levels. Those preferring surgery were more likely to have completed their education by age sixteen, had all tried medical management, and had a greater desire for amenorrhoea. Those without a preference, who were prepared to accept either management tended to fall between the preference groups in terms of their socio-demographic and menstrual history.

The marked differences between the two preference groups highlights the need to look at these groups individually, rather than en masse, as including them all in a single preference group has the effect of equalising their traits. This would almost certainly give rise to misleading information, and would detract from any potential

advantages in generalisability(175,176) gained from including preference groups in studies. The reasons given for having a particular preference also reinforce this view as although there was no treatment bias exhibited by general practitioner's, the media and women's friends both strongly recommended endometrial ablation. The other reasons for preference such as a desire to avoid a general anaesthetic or refusal to take medication because of failure of previous, different medication, are perhaps more obvious, but no less important. Attempts to coerce women with a strong preference for one treatment into having another, especially in the context of a trial will almost certainly lead to patient dissatisfaction, unreliable results and perhaps loss of trust. Baseline traits and outcome for women with heavy periods who have strong treatment preferences are undoubtedly different from each other and also from women without a preference(163).

It will be important to repeat these baseline socio-demographic questions once the Royal College of Obstetricians and Gynaecologists guidelines for the management of menorrhagia in primary care(65) are in widespread use. These in conjunction with the proposed Scottish Intercollegiate Guidelines Network recommendations for the management of menstrual disorders should rationalise primary care management and referral patterns. Once these are established we will be able to detect any changes in baseline traits of women complaining of heavy menstrual loss, duration of level of suffering, treatments received and patterns of referral. Only then will we be able to determine any shifts or changes in practice and whether the guidelines have been effective.

Table 2.1. Socio-demographic and clinical details of women referred with heavy menstrual loss to Aberdeen Royal Infirmary from October 95 to September 96

	Number	Percentage
Total 1st time referrals	273	100
Age		
20 - 29	4	2
30 - 39	88	32
40 - 49	170	62
50 or more	11	4
Marital status		
single	11	4
co-habiting/married	239	88
widowed/separated	22	8
Number of children		
none	19	7
one	27	10
two	120	44
more than two	106	39
Age education completed		
16	118	43
17-18	89	33
19 or older	66	24
Domicile		
rented	5	2
council	72	27
own property	186	70
other	3	1
Occupation		
student	6	2
unemployed	49	18
part-time	107	39
full-time	107	39
housewife	4	2
Smoker		
yes	116	42
Time with heavy menses		
< 6 months	17	6
6 - 12 months	40	15
more than one year	215	79
Days disabled with period		
none	56	22
one	37	14
two or more	167	64
G.P. visits for heavy menses		
one consultation	30	11
more than one consultation	242	89
Treatment received		
none	58	22
medication	210	78
Treatment preference		
none	189	69
prefers medication	36	13
prefers surgery	40	15
reassurance only	8	3

Table: 2.2 Mean HADS and SF-36 scores (95% confidence intervals) for patients referred with heavy menstrual loss

Patient group	number of women	HADS: Anxiety	HADS: Depression	SF-36: Physical functioning	SF-36: Social functioning	SF-36: Role-physical	SF-36: Role-emotional	SF-36: Mental health	SF-36: Energy/ fatigue	SF-36: Pain	SF-36: General health
all women	273	8.19 7.45, 8.93	5.18 4.58, 5.78	79.23 75.67, 82.78	68.68 64.57, 72.80	58.27 51.87, 64.67	58.21 50.81, 65.60	61.02 57.64, 64.41	42.91 39.48, 46.33	56.92 52.74, 61.10	67.36 64.06, 70.67
no preference	189	8.42 7.49, 9.35	5.18 4.50, 5.86	78.33 74.00, 82.65	65.14 60.33, 69.94	55.83 48.14, 63.53	55.19 46.29, 64.08	58.97 54.96, 62.97	41.74 37.97, 45.51	53.83 48.80, 58.86	67.72 63.80, 71.64
preference	84	7.67 6.45, 8.88	5.18 3.89, 6.47	81.25 74.78, 87.72	76.67 69.08, 84.25	63.75 51.88, 75.62	65.00 51.35, 78.65	65.60 59.25, 71.95	45.50 38.10, 52.90	63.89 56.25, 71.25	66.58 60.19, 72.96
prefer medical	36	7.06 5.27, 8.84	4.06* 2.43, 5.68	86.84 77.93, 93.17	85.96* 75.58, 96.34	75.00* 59.44, 90.56	77.19* 60.21, 94.17	71.37** 63.28, 79.45	53.16* 43.31, 63.00	67.84* 57.14, 78.53	66.21 56.34, 76.08
prefer surgical	40	8.19 6.42, 9.96	6.14 4.17, 8.11	76.19 72.85, 84.39	68.25 57.85, 78.65	53.57 35.84, 71.31	53.97 32.79, 75.14	60.38 50.68, 70.08	38.57 27.77, 49.37	60.32 49.52, 71.11	66.90 57.82, 75.99

The eight women preferring reassurance only have not been analysed separately

The eight scales of the SF-36 are scored from 0-100; 0 represents the worst possible and 100 the best possible health.

The two scales of the HADS are scored from 0-21; 0 represents the lowest possible and 21 the highest possible levels of anxiety and depression.

Asterisks denote significant score deviations from the all women group: * $p < 0.05$; ** $p < 0.01$.

Table 2.3 Characteristics of women by preference for treatment

	no preference n = 189	(%)	preference n = 84	(%)	X^2 (d.f.)	significance 2P
Age > 40	127	(68)	54	(63)	0.69 (1)	0.4
Two or more children	163	(87)	63	(73)	10.0 (3)	0.02
Married	163	(87)	76	(88)	0.08 (1)	0.78
Living in own property	126	(67)	60	(70)	0.15 (1)	0.69
Unemployed	40	(21)	19	(22)	0.55 (2)	0.76
Smoker	73	(42)	26	(32)	2.15 (1)	0.14
Heavy periods > 1 year	150	(80)	66	(77)	0.43 (1)	0.51
>1 G.P. consultation for menorrhagia	172	(92)	70	(82)	5.52 (1)	0.02
Previous medical treatment	150	(81)	60	(72)	2.61 (1)	0.11
Disabled for 2 or more days	70	(39)	26	(32)	4.9 (3)	0.18
Hoping for amenorrhoea	14	(7)	10	(12)	0.48 (1)	0.37
H.A.D.S.		**S.D**		**S.D**	**t value**	
anxiety	5.18	(3.8)	5.18	(3.7)	0.0	1.0
depression	8.42	(3.4)	7.67	(3.8)	1.64	0.1

Table 2.4 Characteristics of women by specified treatment preference

	Preferred Medical n =36	(%)	Preferred TCRE n =40	(%)	No preference n =189	(%)	X^2 (d.f.)	significance 2 P
Age > 40	23	(64)	25	(62)	129	(68)	0.65 (2)	0.73
Two or more children	27	(74)	29	(72)	**163**	(86)	6.5 (2)	0.048
Married	34	(95)	32	(81)	163	(87)	3.38 (2)	0.18
Education completed at age 16	14	(38)	23	(58)	81	(43)	5.13 (2)	0.07
Living in own property	**30**	(83)	24	(60)	126	(67)	44.5 (2)	< 0.001
Unemployed	8	(21)	4	(10)	40	(21)	2.8 (2)	0.25
Smoker	16	(44)	13	(33)	73	(39)	1.2 (2)	0.5
Heavy periods > 1 year	32	(89)	36	(90)	150	(79)	3.8 (2)	0.14
>1 G.P. consultation for menorrhagia	32	(89)	36	(90)	172	(91)	0.17 (2)	0.91
Previous medical treatment	22	(61)	**40**	(100)	150	(79)	18.0 (2)	< 0.001
Disabled for 2 or more days	16	(44)	27	(67)	122	(67)	5.7 (2)	0.05
Hoping for amenorrhoea	0	(0)	**10**	(25)	14	(7)	16.4 (2)	< 0.001
H.A.D.S.		**S.D.**		**S.D.**			**F value (d.f.)**	
anxiety	7.06	(3.6)	8.19	(3.8)	8.42	(3.8)	1.96 (2)	0.19
depression	**4.06**	(3.3)	6.14	(4.3)	5.18	(3.4)	3.28 (2)	0.04

Figure 2.1 SF-36 scores for all new referrals with heavy menses and actual normative values with - 1 standard deviation (SD), for the healthy female UK population.

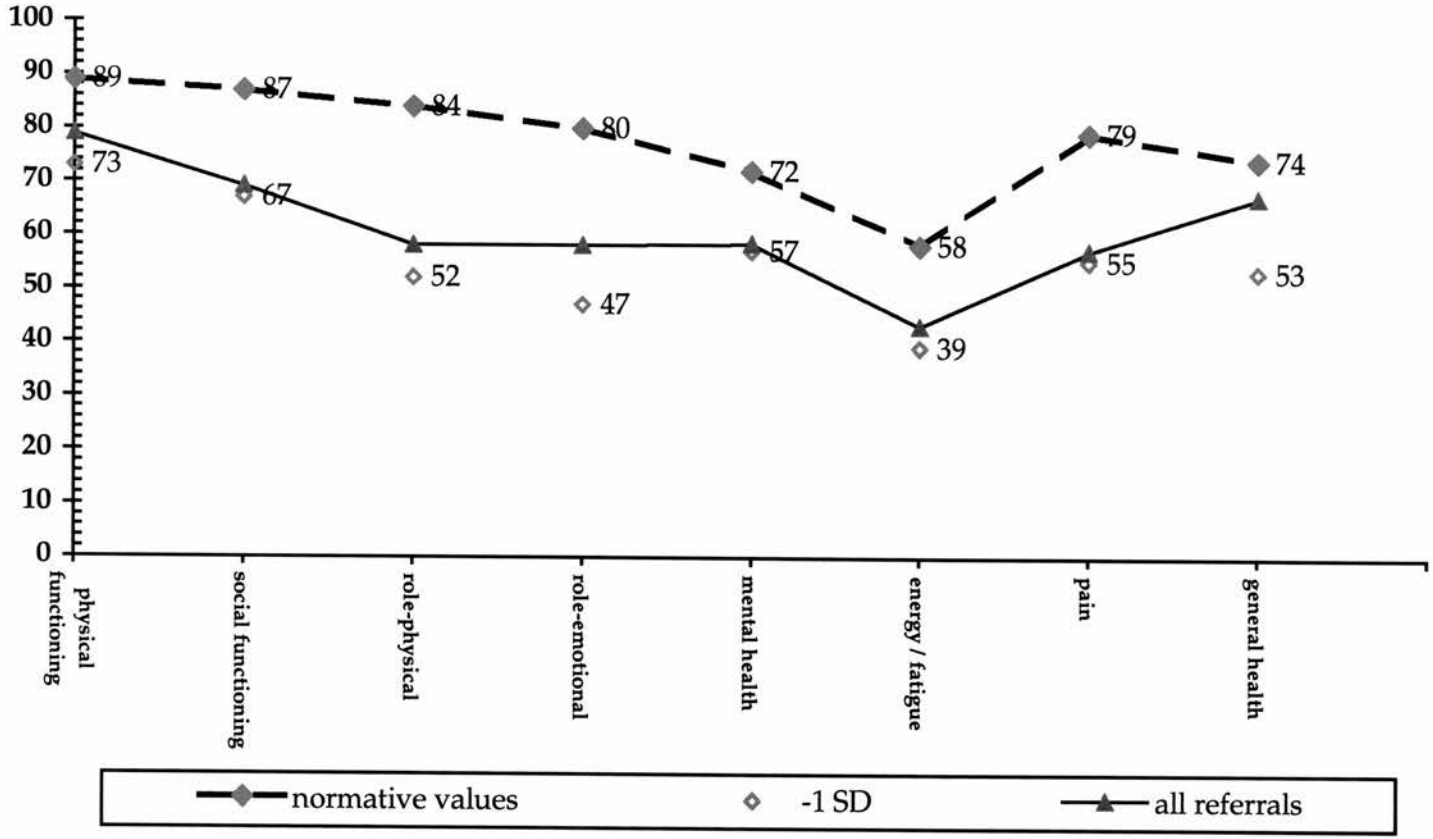
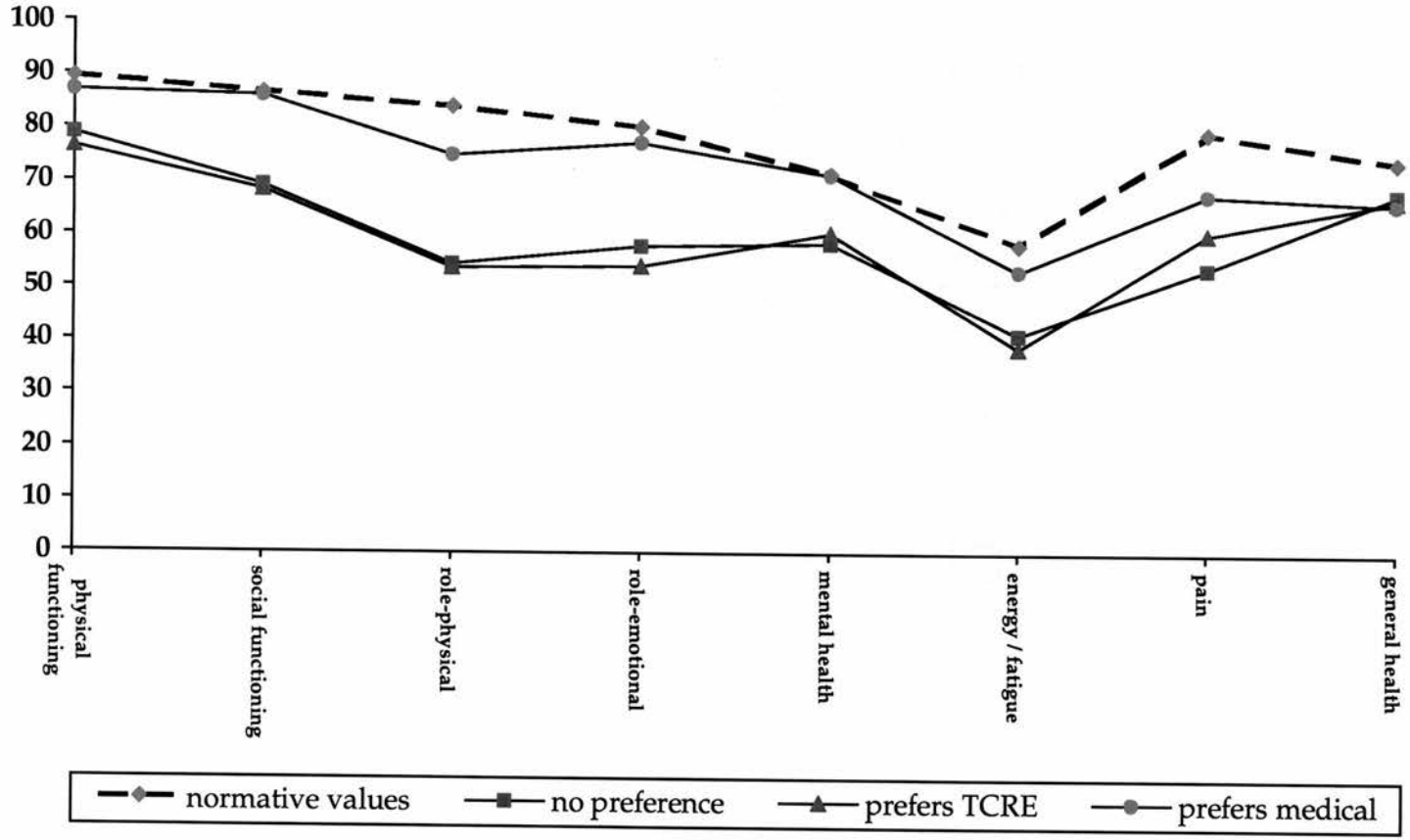


Figure 2.2: a comparison of the SF-36 scores of the preference groups with normative values for the U.K. female population



Chapter 3

A Randomised Controlled Trial Comparing Medical Management with Transcervical Resection of the Endometrium for Women with Heavy Menstrual Loss:

Patients, methods and outcomes at four months

INTRODUCTION

Heavy menstrual loss is a common complaint accounting for between 8% (Chapter 2), and 12%(47) of all new referrals to gynaecology out patient departments. Traditionally, many of these women are initially prescribed medical treatments by gynaecologists. A number of these drugs have been shown to reduce blood loss in a significant proportion of women with objectively proven menorrhagia(20,22,23,68,77,79,80,85). The majority of women who seek treatment for their heavy menstrual loss do not have greater than average menstrual loss(29-31,48). In addition, without a simple and acceptable method of measuring menstrual blood loss, those with pathological loss are difficult to identify. There has been little work undertaken to determine the effects of these medications on women with subjectively heavy menstrual loss. There is also a paucity of data pertaining to the acceptability of these treatments, and whether they improve health related quality of life on women with heavy menstrual loss.

Amongst women seeking surgery, hysteroscopic techniques for endometrial ablation, such as transcervical resection of the endometrium (TCRE), have been shown to be effective, achieving high rates of patient satisfaction(105,106,118,177). Present recommendations are that these techniques are offered as an alternative to hysterectomy once medical managements have failed(118). The pragmatic(89,90) randomised comparison of medical treatment with TCRE, described in this chapter, was undertaken to clarify the place of hysteroscopic surgery in the management of women when first referred to a gynaecologist with heavy menstrual loss. The women

who participated were equally willing to accept medical or hysteroscopic management, as those with a treatment preference had been identified (chapter 2).

PATIENTS AND METHODS

Eligibility

Women were eligible for this trial if consulting a gynaecologist for the first time with a complaint of heavy menstrual loss, their family was complete, they had a clinical diagnosis of dysfunctional uterine bleeding (uterus less than ten weeks pregnancy size and normal endometrial pathology) and had not been referred specifically for surgery. They also had to be willing to be randomised to either medical or hysteroscopic management.

Sample size

Based on expected satisfaction rates of approximately 80% at four to six months after transcervical resection of the endometrium(105,106,118) it was calculated that a minimum of 180 women would be required to have 80% power to detect an absolute difference in satisfaction of 20% at the 5% level of significance(178).

Recruitment

With local research ethics committee approval, women were recruited from the gynaecology clinics of nine of the eleven consultants at this large teaching hospital between October 1994 and September 1995. All women were seen routinely at the

outpatient clinic and if eligible were given a TCRE description sheet (Appendix 3.1), a standard patient information sheet (Appendix 3.2), and were then seen and counselled by the same researcher, Dr K G Cooper. As this was a pragmatic study, preoperative assessment by scan or hysteroscopy was not routinely performed. Initial clinical assessment of uterine size and if indicated, endometrial biopsy were used as criteria for eligibility. Women were randomly allocated to either "transcervical resection" or "medical treatment" by opening sealed, serially numbered, opaque envelopes; the order was determined by computer generated random numbers within balanced blocks of twenty.

Protocol

After giving informed consent, a clinical questionnaire (Appendix 3.3), Short Form 36(146,170) (SF-36), (Appendix 1a), and the Hospital Anxiety and Depression Scale(172) (HADS), (Appendix 1b), were completed and blood was taken for haemoglobin estimation. Bleeding and pain scores were determined by assigning a score from zero to five for heaviness of bleeding or severity of pain for each menstrual day, for a maximum of ten days.

Those women allocated to the medical arm had their treatment chosen by the senior gynaecologist responsible for the clinic. The medication prescribed had to be a recognised treatment for menorrhagia, which should not have been used by the patient before, and was to be continued for at least three cycles.

Patients allocated surgery received an injection of the gonadotrophin releasing hormone analogue, goserelin 3.6 mg. Five weeks later they were admitted under the care of one of the three participating gynaecologists who performed hysteroscopic surgery. Transcervical resection of the endometrium was performed under general anaesthesia using rollerball coagulation to the fundus and cornua with resection of the cavity walls using a 90 degree, 7 mm diameter loop, with 1.5% glycine solution as the distending medium, as described in the introductory chapter.

Patients were reviewed at four months when they self completed questionnaires prior to a formal consultation (Appendix 3.4). The baseline questionnaires, except for HADS, were repeated to assess outcome. Additional questions to establish satisfaction with, and acceptability of treatment (using direct questioning and by Semantic Differential Technique(174) (SDT), (Appendix 1c), were included. At the following consultation, subsequent management preference was ascertained. If further treatment was requested then an appointment with their own consultant was made, otherwise they were discharged to their general practitioner.

Statistics

Data was entered onto a database created on SPSS for windows, and all analyses were undertaken using this programme or by InStat version 2 (GraphPad software). Analysis was by intention to treat; that is women remained in their initial allocated group irrespective of subsequent treatment received. Independent and paired t tests were used for continuous variables (independent and related) with a normal

distribution and the Mann-Whitney U test for ordinal or non-parametric continuous variables. Chi-square test was used for independent nominal data and McNemars test for paired data describing dichotomous variables. Secondary analyses were stratified according to the number of medical treatments' used prior to gynaecological referral.

RESULTS

One hundred and eighty seven (69%) from 273 eligible women participated, 94 allocated to medical treatment and 93 to transcervical resection. The majority of those who refused randomisation had a preference for one or other treatment (see chapter 2). All women but one were assessed at follow up at an average of nineteen weeks after treatment was initiated.

Patient characteristics

The participants are described in table 3.1; the trial groups had similar expectations of treatment and were also of equivalent height, weight and social status. Almost 80% in each arm were employed with about 30% in each group requiring time off work because of menstrual symptoms. Similar numbers had heavy menstrual flow for more than one year (77.6% and 83.8% respectively) whilst 24 of 82 women (29%) in the medical arm and 22 of 85 (26%) in the surgical arm had haemoglobin levels of less than 12 g/dl. Baseline SF-36 scores were also comparable for each group (table 3.6). 22% of women had received no previous medical treatment, 56% one, and 22% more than one, from their general practitioner. 60% of women in both arms reported self treatment

with analgesics perimenstrually. Overall, baseline anxiety scores were elevated (8.96 and 8.85) whereas depression scores were in the normal range (5.62 and 5.32)(172,179).

Medical treatment

Table 3.2 shows the actual treatment prescribed to the medical group. Progestogens were prescribed from day 12 - 25, or 5 - 25 if there was also dysmenorrhoea. The combined oral contraceptive pill preparations recommended were second generation containing 30ug ethinyl oestradiol. Tranexamic acid was prescribed at a dose of 1g four times a day for the first five days of the period in women with regular periods, with mefenemic acid 500 mg three times a day added if there was associated dysmenorrhoea. Danazol was prescribed at a dose of 200 mg a day continuously for ninety days. No women received a treatment that she had previously tried. Progestogens were prescribed to women with heavy and irregular periods, who were unsuitable for, or did not wish to take the combined pill or danazol. 80% of women reported completing the treatment as prescribed, 9% occasionally missing tablets, and 11% stopping medication prior to follow up. There was no significant difference in compliance between the medical treatments used (table 3.2). One woman underwent transcervical resection after continual bleeding for two months on her allocated medical treatment.

Transcervical resection of the endometrium

All those allocated transcervical resection were initially managed this way. The only operative complication was persistent uterine bleeding which occurred in six women.

This abated in all cases following the insertion of a uterine foley catheter at the end of the procedure with removal six hours later. One woman had a two stage hysteroscopic procedure and one woman later had a hysterectomy, both because of submucous fibroids.

Menstrual status at follow up

Transcervical resection of the endometrium reduced bleeding and dysmenorrhoea significantly better than medical treatment (table 3.3, $p < 0.001$ for all variables) and achieved amenorrhoea in 37%. Although the number of heavy days, and bleeding and pain scores, were significantly reduced by medical therapy the effect size was significantly smaller than after surgery. This was reflected in the difference between the groups in changes in mean haemoglobin levels. Medical treatment did not significantly improve any of the five pre-menstrual symptoms, whereas all were significantly improved following transcervical resection.

Satisfaction / acceptability

Transcervical resection resulted in significantly greater levels of satisfaction, symptom improvement and acceptability (table 3.4). Semantic differential rating scores were better on all parameters for hysteroscopic surgery and significantly so for all except pain (table3.5). The commonest reasons for dissatisfaction with medical treatments were no change in the severity of bleeding or pain, although "bad side effects" were cited by twenty seven (45%) of the sixty women who found treatment unacceptable. A total of forty six (48%) in the medical arm and twelve (13%) in the transcervical

resection arm reported symptoms which they considered to be side effects, specifically nausea, headaches and weight gain in the medical group and new pain equally in both groups. One women prescribed danazol suffered a cerebro-vascular accident two months into treatment, whilst another developed hypertension which resolved when medication was stopped.

Health related quality of life

There was significantly greater improvement in all eight subscales of the SF-36 following transcervical resection (table 3.6, figure 3.1). The number of women requiring time off work each month in the medical arm (29%) did not change with treatment, but was significantly reduced ($p< 0.001$), in the surgical cohort (6%).

Secondary analysis stratified by previous medical management

Outcome in respect of bleeding and pain scores, menstrual symptoms, satisfaction, and acceptability was significantly better amongst women allocated hysteroscopic management in all strata characterised by the number of previous medical treatments, including the 22% who had not previously had medical treatment.

DISCUSSION

The results of the hysteroscopic surgery group are clearly better than those of the medically managed group, but are the results trustworthy, and if so to whom do they apply?

Bias between the two study groups in the way that they were selected, if it exists, is likely to be small; the groups were randomly allocated, there was only one loss to follow up, and the groups were similar at entry (table 3.1). Established and recognised questionnaires were used to measure clinical and quality of life parameters, anxiety, satisfaction and acceptability of treatment(106,146,170-172,174,180). It is recognised that these are subjective outcomes. To minimise ascertainment bias, participation in the trial was limited to women who were willing to accept either management. Those who would not accept randomisation were identified and the reasons ascertained (see chapter 2). Some will argue that the optimal medical treatments were not used for each patient and that significant reduction in menstrual blood loss only occurs when the original loss is objectively pathological. In this pragmatic(89,90) trial experienced clinicians prescribed what they regarded to be the most appropriate standard medical treatment for each women (table 3.2). The individual drug therapies were prescribed in doses and timing used in studies demonstrating the effectiveness of these medications(20,22,23,68,77,79,85) or as recommended by the British National Formulary. We would emphasise that 22 out of the 31 patients for whom progestogens were prescribed had these from days 5 to 25 which has been shown to significantly reduce menstrual blood loss(79,80). More specifically no women received progestogens in a dose or timing previously shown to be of little use in the management of menorrhagia(21,78,87). Furthermore, the trial results consistently favoured hysteroscopic management, irrespective of the type of medical treatment prescribed by the gynaecologist or whether medical treatment had previously been tried or not. Although a comparison of TCRE with medical treatment in women who

had received no previous medical treatment would have given a more realistic evaluation of the true treatment effect there are a number of reasons why this was not done. Firstly this is not pragmatic, secondly it is contrary to recommendations of the primary care guidelines(65), and lastly, recruitment would have taken five years to obtain the same numbers. Analysis stratified on the basis of the number of previous treatments received did not show any meaningful differences in primary outcome measures.

Although the medically managed group showed improvement at follow-up this was consistently less than in the resection group. This applied to all assessments of menstrual status, including premenstrual symptoms and dysmenorrhoea (table 3.3). Premenstrual symptoms have previously shown to improve following endometrial ablation(106,181). Satisfaction and acceptability were also clearly higher in the transcervical resection group (tables 3.4 and 3.5), and this was reflected in the numbers of women who would have the same treatment again, would recommend it to another person, and desired further treatment. Transcervical resection of the endometrium achieved satisfaction and acceptability rates which were comparable to those obtained in previous randomised trials(105-107), even though women in this trial were not specifically seeking surgical treatment.

Menorrhagia is known to cause significant deterioration in general health and quality of life(52,171,182,183) which has often been overlooked in the assessment of treatment. The reduced SF-36 scores observed at baseline were consistent with the scores reported

for other women with menorrhagia(52). After medical treatment there were significant improvements in all parameters except for general health, but normal scores were not attained for any of the eight parameters. In contrast, scores equal to or better than normal for all eight SF-36 scales were observed after transcervical resection (table 3.6)(148). This concurs with the findings of Coulter from observational series data(54). Almost 30% of women felt unable to undertake their normal daily work routine because of their period. Whilst this was highly significantly improved following TCRE, the proportion remained essentially unchanged in the medical treatment group. This lack of improvement is difficult to explain in light of the other medical arm outcome measures, but is worrying as the ability to undertake normal daily activities is of paramount importance.

Objective measurement of blood loss was not undertaken as this is not yet routine clinical practice. Semi-quantitative measurement using pictorial blood loss assessment charts(34) would have been useful in this trial potentially giving more meaningful menstrual outcome values than the scoring method used. This would have been helpful in determining those with true menorrhagia and for evaluating the different medical treatments. An assessment of severity of menstrual loss and treatment success was undertaken by measuring haemoglobin level at recruitment and follow up and by calculating menstrual bleeding scores. The significantly greater mean increase in haemoglobin concentration amongst women allocated transcervical resection is consistent with the differences in the subjective measures of outcome.

It is noteworthy that 48% of women in the medical arm reported side effects and over half deemed these unacceptable. None of the six surgical complications was serious. However, these women did undergo a general anaesthetic and the risks associated with hysteroscopic surgery are too uncommon to evaluate reliably in a trial of this size.

These results should be generalisable to women first seeking advice from a gynaecologist for management of heavy menstrual bleeding who have no treatment preference. 70% of those fulfilling the entry criteria agreed to randomisation. Women who refused randomisation had a preference for transcervical resection or medical treatment in equal proportions.

A formal economic evaluation was not conducted. The cost of hysteroscopic surgery has been estimated at £560(145) in the short term, rising to £1012 after four years(151). These costs will be offset to some extent by the expense of medical management. However, the resource implications of introducing transcervical resection of the endometrium to all gynaecological centres and the training requirements involved could be considerable, and these would need to be included in any assessment of cost-effectiveness. Also, new, technically less demanding techniques for ablative techniques that can be undertaken using local anaesthetic have been reported(112,114,184) whilst the progestogen loaded coil seems effective in reducing menstrual loss(80,81). An even more conservative approach could be adopted through reassurance and counselling for those determined to have menstrual loss within normal limits. All these methods of management require formal evaluation in randomised controlled trials before

accepting them as effective advances in the management of women complaining of heavy menses.

This trial indicates that early ablative surgery should be one of the options considered for woman consulting a gynaecologist for the first time seeking treatment of excessive menstrual loss, with the choice made by the woman after a full discussion of the advantages and disadvantages of the various treatment options

PUBLICATION

The above trial was published in the British Journal of Obstetrics and Gynaecology in December 1997(185).

Table 3.1 Baseline characteristics of each randomised group at recruitment. Values are numbers (percentages) of women unless stated otherwise.

	Randomised Medical (n = 94)		Randomised T.C.R.E. (n = 93)	
Mean age (S.D.)	41.4	(5.2)	41.7	(5.2)
Mean haemoglobin g/dl (S.D.)	12.79	(1.19)	12.65	(1.63)
Menstrual symptoms				
irregular periods	49	(52.1)	52	(56.5)
3 - 5 days bleeding	15	(16.0)	11	(11.8)
>5 days bleeding	79	(84.0)	82	(88.2)
mean no. days heavy bleeding (S.D.)	4.56	(2.35)	4.28	(2.22)
regular dysmenorrhoea	53	(56.3)	48	(51.6)
Menstrual symptom rating scale				
mild or moderate	1	(1.1)	0	(0)
severe	59	(62.7)	53	(57.6)
very severe	28	(29.8)	36	(39.1)
Bleeding score - mean -(S.D.)	24.2	(8.5)	25.0	(7.6)
Pain score - mean -(S.D.)	14.7	(9.5)	13.5	(10.7)
Premenstrual symptoms				
bloating	71	(76.3)	75	(82.4)
breast discomfort	65	(69.9)	65	(71.4)
irritability	65	(69.9)	68	(74.7)
headaches	63	(67.7)	54	(59.3)
depression	53	(57)	51	(56)
Hospital Anxiety and Depression Scale (HADS)				
anxiety - mean score (95%C.I.)	8.96	(7.8, 10.1)	8.85	(7.6, 10.1)
depression - mean score (95%C.I.)	5.62	(4.7, 6.6)	5.31	(4.3, 6.5)

Table 3.2 Drug treatments received by those randomised to medical treatment alone, and rates of satisfaction, acceptability and desire to continue the same treatment at follow up. Values are numbers of women (percentages)

	n= 94		Satisfied with treatment		Treatment acceptable		Continue treatment	
Progestogens day 12- 25 / 5- 25	31	(33)	10	(34)	11	(36)	6	(19)
Combined pill	24	(25.5)	8	(33)	8	(33)	6	(25)
Tranexamic acid	22	(23.4)	7	(34)	6	(29)	4	(18)
Danazol	15	(16)	5	(33)	7	(47)	3	(20)
HRT (with NSAID)	2	(2.1)	1	(50)	1	(50)	2	(100)

Progestogens day 5 - 25 = 22 of 31 women, 12 - 25 = 9 of 31 women
HRT = hormone replacement therapy, NSAID = non steroidal anti- inflammatory drug

Table 3.3 Menstrual status and symptoms at 4 months follow up. Values are numbers of women (percentages), unless stated otherwise.

	Randomised Medical n = 93		Randomised T.C.R.E. n = 93		95% C.I. for diff	P value
Mean increase in Hb level, g/dl , (S.D.)	0.18	(1.29)	0.76***	(1.62)	-1.04, -0.12	0.014
Mean increase in Hb if baseline <12 g/dl	0.93**	(1.5)	2.53***	(1.94)	-2.64, -0.56	0.003
Menstrual status						
unchanged or heavier	48	(51.6)	7	(7.5)	33%, 56%	< 0.001
Duration of bleed						
none	3	(3.2)	34	(37)		
< 3 days	3	(3.2)	17	(18.5)	37%, 59%	< 0.001
3 - 5 days	29	(31.2)	24	(26.1)		
>5 days	58	(61.9)	17	(18.5)		
Mean no. of days heavy bleeding (S.D.)	3.15***	(2.8)	0.76***	(1.3)	1.75, 3.03	< 0.001
Bleeding score - mean -(S.D.)	17.8***	(9.15)	5.1***	(6.97)	10.25, 15.29	< 0.001
Pain score - mean -(S.D.)	9.7***	(8.92)	2.8***	(6.14)	4.51, 9.24	< 0.001
Dysmenorrhoea						
same or worse	42	(46.2)	14	(15.3)	18%, 53%	< 0.001
Premenstrual symptoms						
breast discomfort	55	(59.8)	40***	(44.0)	2%, 31%	0.03
bloating	73	(79.3)	53***	(58.2)	8%, 35%	0.002
irritability	62	(67.4)	49**	(53.8)	1%, 28%	0.06
headaches	57	(62.0)	34**	(37.4)	11%, 39%	< 0.001
depression	51	(55.4)	21***	(23.1)	19%, 46%	< 0.001

Asterisks denote changes from baseline (*p < 0.05, **p < 0.01, ***p < 0.001)
Hb = haemoglobin (<12 g/dl), n = 78 (24) medical, n = 82 (22) T.C.R.E.
95% C.I. for diff = 95% confidence intervals for difference in means or proportions(%).

Table 3.4 **Patient satisfaction, menstrual symptom rating scale, effectiveness and acceptability of treatment and desired future treatment. Values are numbers of women (percentages) unless stated otherwise.**

	Randomised Medical n = 93		Randomised T.C.R.E n = 93		95% C.I. for diff	P value
Satisfaction with treatment						
totally / generally satisfied	25	(26.8)	70	(76.0)	-61%, -36%	< 0.001
Effect of treatment on symptoms						
cured/acceptable improvement	29	(32.2)	77	(84.9)	-64%, -40%	< 0.001
Menstrual symptom rating scale						
none	2	(2.2)	34	(37)	-45%, -24%	< 0.001
mild or moderate	39	(41.9)	51	(53.4)		
severe	42	(45.2)	6	(6.5)		
very severe	10	(10.8)	1	(1.1)		
Was the treatment acceptable?						
yes	33	(35.5)	85	(93.4)	-67%, -45%	< 0.001
Prepared to have same treatment again						
yes	29	(31.2)	86	(92.5)	-72%, -51%	< 0.001
Would you recommend your treatment?						
yes	38	(40.9)	84	(90.3)	-61%, -38%	< 0.001
Require days off work?						
no	56	(70.9)	73	93.6**	-31%, -5%	< 0.001
Treatment desired						
none	3	(3.2)	82	(88.1)	-92%, -78%	< 0.001
medical (same or different)	40	(43.0)	5	(5.4)		
t.c.r.e.	49	(52.7)	2	(2.2)		
hysterectomy	1	(1.1)	4	(4.3)		

Asterisks denote significant changes from the baseline (*p < 0.05, **p <0.01, ***p <0.001)
95% C.I. for diff = 95% confidence intervals for difference in proportions(%)

Table 3.5 Semantic differential rating scores for acceptability of treatment (score -3 [best] → +3 [worst])

	Medical n = 93		T.C.R.E. n = 93			
Adjectival pair	**Mean**	**S.D.**	**Mean**	**S.D.**	**95% C.I. diff**	**Significance**
painless - painful	-0.44	(1.74)	-0.71	(1.79)	-0.25, 0.78	$p = 0.3$
happy - sad	-0.12	(1.56)	-1.42	(1.43)	0.87, 1.74	$p < 0.001$
pleasant - unpleasant	0.11	(1.55)	-0.58	(1.33)	0.27, 1.10	$p = 0.002$
positive - negative	-0.14	(1.81)	-1.80	(1.44)	1.19, 2.14	$p < 0.001$
safe - dangerous	-0.68	(1.65)	-1.75	(1.21)	0.65, 1.49	$p < 0.001$
attractive - unattractive	0.01	(1.04)	-0.40	(0.89)	0.13, 0.69	$p = 0.004$
mild - harsh	-0.52	(1.41)	-1.12	(1.32)	0.21, 1.00	$p = 0.003$
agreeable - disagreeable	-0.23	(1.92)	-1.30	(1.39)	0.59, 1.57	$p < 0.001$
active - passive	-0.23	(1.12)	-0.77	(1.24)	0.20, 0.89	$p = 0.002$
easy - hard	-1.01	(1.79)	-1.58	(1.41)	0.11, 1.04	$p = 0.016$
fast - slow	-0.23	(1.69)	-1.69	(1.35)	0.88, 1.77	$p < 0.001$
good - bad	0.02	(2.03)	-2.09	(1.34)	1.61, 2.61	$p < 0.001$

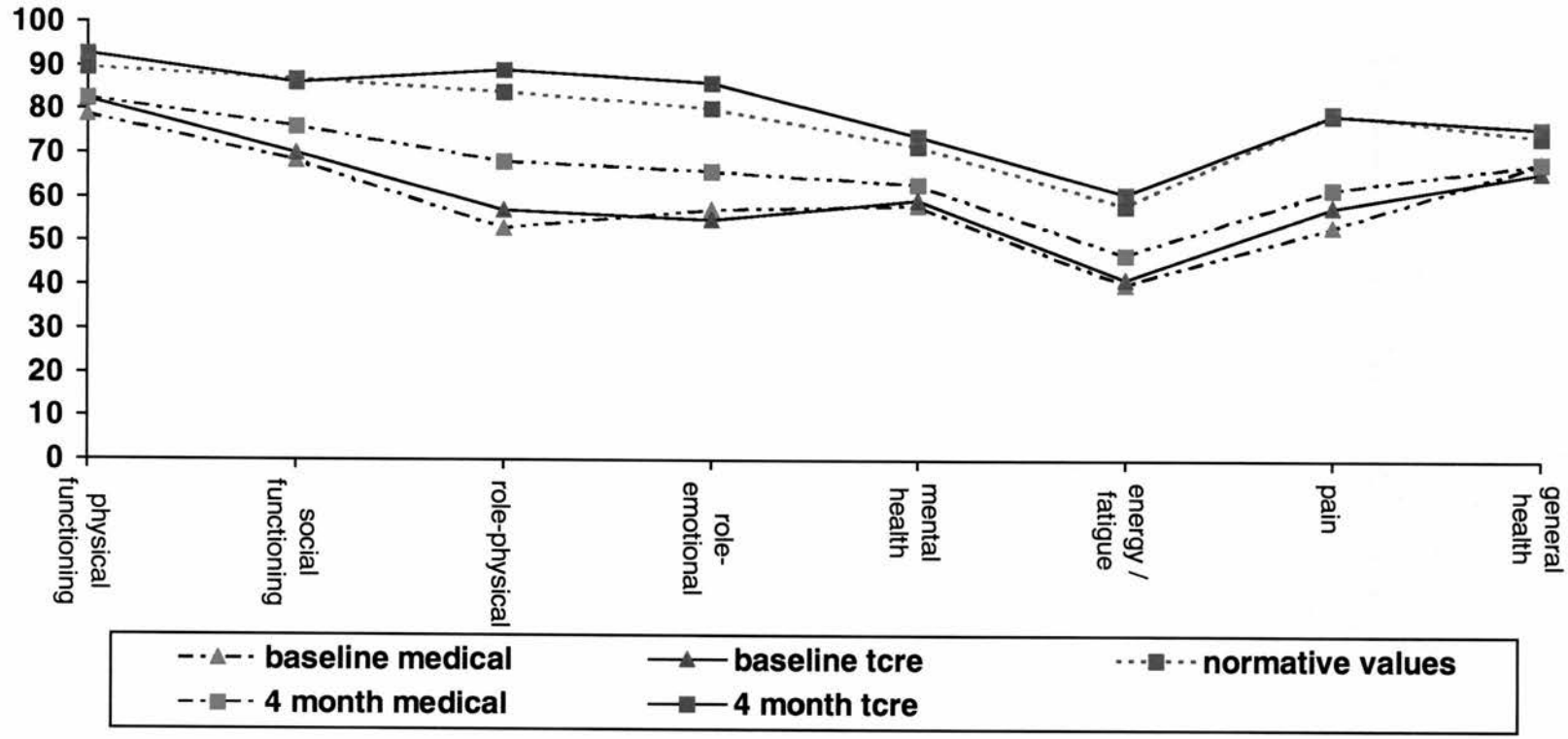
95% C.I. diff = 95% confidence intervals for difference in means

Table 3.6 **Short Form 36 Health Survey Questionnaire :- mean baseline scores and change in score at four month follow up. Scores range from 0 → 100 (worst → best)**

	Medical n = 93		T.C.R.E. n = 93		
	mean	S.D.	mean	S.D.	P value
Short Form 36 - baseline scores (S.D.)					
physical functioning	78.88	(20.72)	81.94	(19.38)	0.30
social functioning	69.10	(20.98)	69.06	(24.29)	0.99
role - physical	54.26	(37.86)	56.72	(39.38)	0.66
role - emotional	57.80	(42.10)	53.41	(44.00)	0.49
mental health	58.32	(18.27)	59.14	(19.08)	0.77
energy/fatigue	41.24	(16.84)	41.51	(19.22)	0.92
pain	53.8	(24.84)	57.95	(25.16)	0.26
general health	68.02	(18.85)	65.10	(20.05)	0.31
Short form 36 - change in score (S.D.)					
physical functioning	4.84*	(16.72)	10.16**	(16.51)	< 0.05
social functioning	7.57*	(26.26)	17.44**	(25.08)	< 0.05
role - physical	15.32*	(46.78)	32.26**	(38.23)	< 0.01
role - emotional	8.96*	(49.43)	31.54**	(45.94)	< 0.01
mental health	4.78*	(16.69)	15.01**	(19.00)	< 0.01
energy/fatigue	7.07*	(20.23)	20.53**	(20.76)	< 0.01
pain	8.84*	(26.39)	21.62**	(31.33)	< 0.01
general health	-0.25	(15.99)	10.49**	(20.85)	< 0.01

Asterisks denote significant changes from the baseline (*$p < 0.05$, **$p < 0.01$)

fig. 3.1. Short Form 36 scores



Chapter 4

A Randomised Controlled Trial Comparing Medical Management with Transcervical Resection of the Endometrium for Women with Heavy Menstrual Loss:-

clinical and quality of life outcomes at 24 months

INTRODUCTION

Medium and long term follow-up data are now available for hysteroscopic endometrial ablative techniques for women who would otherwise have undergone hysterectomy(55,107,151). In contrast, there is a paucity of follow-up data of longer than six months for women prescribed medical treatment for menorrhagia(51) and evidence that problematic menses recur on cessation of therapy(30,186). The majority of trials assessing medical treatments also adopt an explanatory, rather than pragmatic(89,90) approach to investigation, the emphasis being on reduction in measured menstrual blood loss in women with proven pathological loss (>80mls/cycle). This represents less than half of all women complaining of heavy menstrual loss(24,48) and of those referred for endometrial ablation(187). Few medical studies have assessed satisfaction with, and acceptability of, treatment, or the women's desire to continue the same treatment. More importantly, other than this trial, no studies have evaluated the effect of medical treatments on health related quality of life despite strong evidence that women complaining of heavy menstrual loss suffer a significant reduction in this(52,171) (chapter 2).

The short term results of this randomised trial comparing medical treatment with TCRE for women first attending a gynaecologist for treatment of heavy menstrual loss have been reported in chapter 3. The trial recruited women who were not specifically referred for surgical treatment and who were equally prepared to have medical treatment or TCRE. This chapter presents the two-year follow-up of these women, re-

evaluating their outcomes with respect to subsequent treatments received, satisfaction with and acceptability of treatment, and change in health related quality of life.

PATIENTS AND METHODS

Eligibility

Full details of the original trial design, treatment allocation, and outcome measures at four months have been reported and are described in the previous chapter. In summary, women were eligible if they met the following entry criteria: consulting a gynaecologist for the first time with a complaint of heavy menstrual loss; family complete; a clinical diagnosis of dysfunctional uterine bleeding (uterus less than ten weeks pregnancy size and normal endometrial pathology); and had not been referred specifically for surgery. They also had to have no preference for either medical or hysteroscopic management. One hundred and eighty seven (69%) from 273 eligible women consented to randomisation, 94 allocated to medical treatment and 93 to transcervical resection. The majority of those who refused randomisation had expressed a preference for one or other treatment and have been reported separately(163). After follow-up at four months, all recruits, irrespective of initial management, could request further and/or different treatment. This policy reflected normal clinical practice in keeping with the pragmatic design of the trial.

Protocol

Postal questionnaires (Appendix 4.1) were sent two years after initial treatment assessing gynaecological symptoms, satisfaction with treatment, and acceptability of management. Changes in health related quality of life were measured using the SF-36 health survey(146,170) (Appendix 1a). Subsequent and additional treatments received were also determined, both from the questionnaire and from the hospital surgical database. As this is the only hospital with a gynaecological service for the district, we can be certain of further hospital treatment received for those who had not left the Grampian region of Scotland.

Sample size

The original sample size calculations (Chapter 3), indicated that a minimum of 180 women would be required to have 80% power to detect an absolute difference in satisfaction with treatment of 20% at the 5% level of significance(178).

Statistics

Data was entered onto a database created on SPSS for windows, and all analyses were undertaken using this programme or by InStat version 2 (GraphPad software). Analysis was by 'intention to treat', that is women remained in the group to which they were originally allocated, irrespective of subsequent treatment received. Independent and paired t-tests were used for continuous variables (independent and related) with a normal distribution, and the Mann-Whitney U test for ordinal or non parametric continuous variables. The Chi-square or Fisher's Exact test were used for independent

nominal data, and McNemar's and Wilcoxon's tests for paired nominal data describing dichotomous and related variables respectively.

RESULTS

One hundred and eighty seven women were originally recruited between October 1994 and November 1995, 94 randomised to have medical treatment and 93 to TCRE. Postal follow-up questionnaires two years (range 23 to 28 months) after initial treatment were completed by 173 (92%) women, 86 in the medical group and 87 in the TCRE group. Six of the fourteen not followed-up were known to have left the region.

Patient Characteristics

Table 4.1 summarises the baseline characteristics of those successfully followed-up; they were very similar to the total trial group (table 3.1, chapter 3). At the time of recruitment, almost 80% in each group were employed with about 30% requiring time off work because of menstrual symptoms. Similar numbers had heavy menstrual flow for more than one year (78% and 84% respectively). Hospital Anxiety and Depression Scale (HADS) anxiety scores were elevated (9.35 and 8.78) whereas depression scores were in the normal range (5.76 and 5.29)(179). Baseline SF-36 scores were also comparable for each group all eight variables were reduced relative to women of the same age in the general population(148) (figure 4.1 & table 4.6). Complete details, including medical treatments received, are described in the previous chapter.

Subsequent treatment received or continued at two years

Subsequent management is summarised in table 4.2. At two-year follow-up, 59% of those randomised to medical treatment had undergone TCRE, hysterectomy or both, and 82% of the initial operations had been undertaken within twelve months of trial entry. 21% remained on medical treatment, although specific medications were not determined. 17% of women allocated to TCRE had undergone repeat TCRE, hysterectomy or both. One hysterectomy, in the TCRE arm, resulted from an emergency laparotomy performed for acute sepsis and generalised peritonitis, secondary to bilateral rupture of pyosalpinges, in an amenorrhoeic woman, 14 months after initial TCRE. No women requested further surgery or medication after completing the questionnaire. Operative data were obtained from the hospital surgical database for the fourteen participants who did not complete two-year questionnaires. Of eight women in the medical arm, four had undergone TCRE; amongst six in the TCRE arm, one hysterectomy had been performed.

Menstrual status at follow-up

Changes in menstrual symptoms at two years are shown on table 4.3. There was a highly significant and comparable reduction in bleeding and pain scores in both trial groups. 60% of the medical arm and 64% of the TCRE arm reported no new pelvic pain of any kind. 42% of those in the medical arm were either amenorrheoic or had very light periods (spotting or bleeding score from 1 to 5), compared with 60% of the TCRE arm ($p= 0.02$). Significantly fewer women in the TCRE arm regarded their menstrual status as unchanged or worse. Significant reductions were present in three of the five

premenstrual symptoms in the medical arm, whereas these had not been detected at four months. Significant reductions in all five pre-menstrual symptoms in the TCRE arm were evident, but with the exception of headaches and irritability, these benefits were less than at four months. Overall there was no significant difference in premenstrual symptoms between the two study groups.

Satisfaction / acceptability

Compared with the medical group, women allocated TCRE had significantly higher levels of satisfaction and symptom improvement; they were also more likely to find their treatment acceptable (table 4.4). These values were much improved in the medical arm from the four month data, whereas those for TCRE were similar. Only 24% of women allocated to medical treatment would recommend this form of treatment, compared with 78% in the surgical arm who would recommend TCRE ($p<0.001$, difference -54%, 95% C.I. -66% to -44%). Of the 47 women in the medical arm who underwent a TCRE, 40 (85%) of them would recommend this form of treatment.

Health related quality of life

Baseline and two-year SF-36 follow-up data are presented for women who had completed both questionnaires (table 4.5). Change in SF-36 scores were higher for all health scores at two years for those allocated TCRE, but not significantly so. Women in the medical arm scored better than at baseline and significantly so for five of the eight variables, in addition there was an overall improvement from four-month scores. Seven of the eight health scores were significantly improved from baseline in the TCRE

group, but scores were lower than those obtained at four months. Figure 4.1 shows how the follow-up scores compare with baseline and with normative values for a healthy female population of equivalent age(148). The number of working women who were taking time off work each month because of their periods was significantly, and comparably reduced from 30% at recruitment to 14% in the medical arm and to 10% in the surgical group at two years ($p = 0.1$, 95% C.I. of difference -5% to 15%).

DISCUSSION

This study represents the longest follow-up of women participating in a randomised trial of medical treatment for women with heavy menstrual loss. It is also the longest follow-up of women undergoing TCRE who were not initially referred for surgical treatment of their periods. Its other strength is that the randomised cohorts are not distorted by motivational bias, as those preferring treatments were identified at and excluded at the outset (Chapter 2). This has allowed us to observe the treatment progression in both arms in the knowledge that requests for TCRE's from those in the medical arm have not resulted through "resentful demoralisation"(175), that is, disappointment at their initial allocation. Analysis was by intention to treat and therefore no women changed trial arms or were withdrawn from the study because of subsequent treatments received.

Follow-up questionnaires were not obtained for eight women from the medical arm and six from the TCRE arm. Since this is the only hospital offering gynaecological

services in the area, information on operative procedures, general practitioner correspondence, and subsequent clinic attendance for these women was available. It is unlikely that loss of 8% of the trial women has affected the generalisability of the results as the further surgical treatment received by these women was similar to those who were followed-up.

Medical arm

Only 21% of women initially allocated to take medical treatment continued to take this at two years, although 41% of women in this group had avoided surgical treatment. Individual medical treatments used by women at follow-up were not determined as it was the aim of the trial to evaluate a medical policy rather than identify optimal medical treatment. Stratified analysis on the basis of subsequent treatment received in the medical arm, is also methodologically unsound, in view of the small numbers and inherent bias created as many women eventually chose their subsequent treatments. Satisfaction with, and acceptability of, treatment were much improved from four months, but remained significantly less than amongst those allocated to TCRE. Bleeding and pain scores were significantly less than at four months and were comparable to the TCRE arm. Other menstrual parameters were also significantly improved, but pelvic pain remained low and equivalent in both arms. These improvements from the four-month results may be due to the 59% of women in this arm who underwent TCRE or hysterectomy. Nevertheless, those women avoiding surgical treatment can be presumed to be equally satisfied as they were aware that surgery was available had they requested it. The fact that only 24% of women would

recommend medical treatment compared to 85% (40/47) of those who subsequently underwent TCRE in the medical arm, who would recommend TCRE, strengthens the argument that TCRE has improved the medical arm results.

Surgical arm

17% of women in the TCRE arm had undergone surgical retreatment at two years, less than reported in previous randomised single-centre trials comparing TCRE with hysterectomy(55,151), but similar to the multi-centre MRC trial(107). These differences between the trials mounted in our centre may represent variation at recruitment in both severity of symptoms, and expectations of treatment, as women in this trial were excluded from randomisation if initial referral was for surgical treatment. Satisfaction with, and acceptability of, treatment remained high at about 80%, comparable to the four-month follow-up, and significantly better than amongst women in the medical arm. This also correlated well with the numbers who would recommend TCRE (78%) as treatment for heavy menstrual loss. Bleeding and pain scores and number of heavy days remained highly significantly better than at recruitment, similar to four-month levels, with only the number of days heavy bleeding significantly less than amongst those in the medical arm. The results for the surgical cohort are comparable to results of previous trials assessing endometrial ablation(104-107), the important difference being that these were women not initially seeking surgical treatment. Most importantly, women in the surgical arm did not have higher hysterectomy rates than those in the medical arm (10% v. 14%, 95% C.I. -16 to 4%), suggesting that early recourse to TCRE does not increase the risk of hysterectomy.

Health related quality of life

This trial represents the longest term evaluation of change in health related quality of life for women with heavy menstrual loss. It could be argued that this should be the definitive arbiter of treatment success, and its measurement was recommended by the effective health care group(51) for outcome assessment of treatments for menorrhagia. Heavy menstrual loss is known to cause significant deterioration in general health and quality of life(52,171,185) which has often been overlooked in the evaluation of treatment. The reduced SF-36 scores observed at baseline were consistent with the scores reported for other women with menorrhagia(52). For women in the TCRE arm, two-year health related quality of life scores, as measured by SF-36, remain at near normative levels(148), are highly significantly improved from baseline for seven of the eight health scales, and are similar to values obtained at two years post TCRE by Sculpher et al(55). The scores are however, globally reduced from the four-month results. One possible explanation is an initial high score achieved in a "honeymoon" period occurring soon after relief of symptoms. Another is that there has been a genuine fall off in the benefits of the operation, although this is not borne out by the satisfaction and menstrual status results. Women in the medical arm also had higher SF-36 scores than at baseline, but these remained lower than scores achieved in the TCRE arm and substantially lower than normative values (figure 1). The increased scores in the medical arm from the four-month data may reflect the number of women undergoing surgical treatment since then.

Patient preference

Women who exhibited a preference and who chose their treatments were not followed up by questionnaire at two years because of the small numbers involved and the difficulties analysing data from non-randomised observational cohorts. Nonetheless, subsequent treatments received were determined from hospital records. Those preferring TCRE at outset had a markedly higher re-operation rate than amongst those randomised to TCRE (42% v. 17%). This is likely to reflect different expectations of treatment amongst those preferring surgical treatment (chapter 2)(163), and indicates that these should be clearly determined at outset, with hysterectomy discussed with women wanting amenorrhoea. In contrast, of the women preferring medical treatment, only two had undergone TCRE and none a hysterectomy, a much lower proportion than those randomised to medical treatment (54% TCRE, 14% hysterectomy). This confirms that those women with a strong preference for medical treatment have a good chance of avoiding surgery, and can be encouraged to pursue this option.

Conclusion

At two years, women allocated to TCRE are still in better health than those initially managed medically. The results therefore consolidate the conclusions made from the four-month data and the findings apply to those women attending a gynaecologist for the first time, for treatment of heavy menstrual loss, who do not have a treatment preference. Early recourse to hysteroscopic surgery will afford these women better relief of symptoms and improvements in health related quality of life. Reassuringly,

over 80% of those managed by TCRE at outset have avoided further surgical treatment and there was no detectable increase in hysterectomy rates at two years in this group compared with those randomised to medical therapy. Nevertheless, 40% of women in the medical arm have not undergone surgical treatment for their complaint, although only half of these women continue to take any medical therapy. Alternative, promising, non-surgical treatments, such as the Mirena coil(82), or less invasive surgical techniques, such as microwave ablation(114) or thermal balloon(164,165), should be evaluated in well constructed randomised trials, comparing them with a rigorously evaluated hysteroscopic surgical technique, before accepting them as effective alternative managements for menorrhagia.

PUBLICATION

The above trial was published in the British Journal of Obstetrics and Gynaecology in March 1999(188)

Table 4.1 Baseline characteristics of each randomised group at recruitment. Values are numbers (percentages) of women unless stated otherwise

	Randomised Medical (n = 86)		Randomised T.C.R.E. (n = 87)	
Mean age (S.D.)	41.4	(5.4)	41.9	(5.1)
Mean haemoglobin g/dl (S.D.)	12.79	(1.16)	12.61	(1.66)
Menstrual symptoms				
irregular periods	45	(52)	49	(58)
3 - 5 days bleeding	14	(16)	9	(11)
>5 days bleeding	72	(84)	78	(89)
mean no. days heavy bleeding (S.D.)	4.6	(2.43)	4.24	(2.19)
regular dysmenorrhoea	53	(56)	48	(52)
Menstrual symptom rating scale				
mild or moderate	6	(7)	4	(4)
severe	54	(63)	51	(59)
very severe	26	(30)	32	(37)
Bleeding score - mean -(S.D.)	24.7	(8.6)	24.8	(7.3)
Pain score - mean -(S.D.)	15.2	(9.6)	13.3	(10.2)
Premenstrual symptoms				
bloating	64	(75)	70	(82)
breast discomfort	60	(71)	63	(74)
irritability	60	(71)	64	(75)
headaches	57	(67)	57	(61)
depression	49	(58)	50	(59)
Hospital Anxiety and Depression Scale (HADS)				
anxiety - mean score (95%C.I.)	9.35	(8.47 to 10.22)	8.78	(7.85 to 9.70)
depression - mean score (95%C.I.)	5.76	(5.06 to 6.45)	5.29	(4.54 to 6.05)

Table 4.2 Subsequent management of those followed-up at 2 years. Values are numbers (percentages) of women

	none	medical	TCRE	repeat TCRE	hysterectomy	TCRE & hysterectomy
Medical, n = 86	18 (21%)	17 (20%)	38 (44%)	0	4 (4%)	9 (10%)
TCRE, n = 87	65 (75%)	7 (8%)		6 (7%)	5 (6%)	4 (4%)

Table 4.3 Menstrual status and symptoms at two- year follow-up. Values are numbers of women (percentages), unless stated otherwise.

	Medical n = 86		T.C.R.E. n = 87		95% C.I. for difference	P value
Menstrual status						
unchanged or heavier	16	(18)	5	(6)	3 to 22%	0.02
Duration of bleed						
none	26	(30)	33	(38)	-22 to 6%	
1 - 3 days	3	(9)	14	(16)	-16 to 4%	0.5
3 - 5 days	49	(52)	31	(36)	-4 to 21%	
>5 days	8	(9)	9	(10)	-8 to 20%	
Mean no. of days heavy bleeding (S.D.)	2.0***	(2.8)	1.1***	(1.3)	0.37 to 1.4	0.001
Bleeding score - mean -(S.D.)	6.8***	(9.9)	5.4***	(8.1)	-1.4 to 4.1	0.33
Pain score - mean -(S.D.)	4.1***	(7.4)	3.9***	(7.5)	-2.1 to 2.4	0.9
Dysmenorrhoea - same or worse	25	(29)	20	(23)	-7 to 19%	0.46
Dyspareunia - same or worse	9	(11)	5	(6)	-3 to 13%	0.1
Premenstrual symptoms						
breast discomfort	47*	(58)	49**	(58)	-17 to 13%	0.96
bloating	57	(70)	55**	(65)	-11 to 17%	0.44
irritability	55	(68)	47**	(55)	-5 to 25%	0.09
headaches	43*	(53)	34**	(40)	-4 to 26%	0.09
depression	30***	(37)	28***	(33)	-11 to 17%	0.58

Asterisks denote changes from baseline (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$)
95% C.I. for difference = 95% confidence intervals for difference in means or proportions(%).

Table 4.4 Patient satisfaction, effectiveness and acceptability of treatment, and recommended treatment. Values are numbers of women (percentages) unless stated otherwise.

	Medical n = 86		T.C.R.E n = 87		95% C.I. for difference	P value
Totally or generally satisfied with treatment	48	(57)	68	(79)	-36 to -9%	0.002
Cure or acceptable improvement in symptoms	53	(59)	69	(81)	-31 to -4%	0.017
Treatment acceptable	65	(77)	79	(93)	-26 to -4%	0.004
What treatment would you recommend to a friend?						
none	15	(17)	9	(11)		
medical	21	(24)	2	(2)		
TCRE	40	(47)	68	(78)	-61 to -33%	< 0.001
hysterectomy	10	(12)	8	(9)		

Asterisks denote significant changes from the baseline (*p < 0.05, **p <0.01, ***p <0.001)
95% C.I. for difference = 95% confidence intervals for difference in proportions(%)

Table 4.5 Short Form 36 Health Survey Questionnaire :- mean baseline scores and change in score at two-year follow up. Scores range from 0 → 100 (worst → best)

	Medical n = 83		TCRE n = 86				
	mean	SD	mean	SD	difference	P value	95% C.I.
Short Form 36 - baseline scores (S.D.)							
physical functioning	78.67	(21.14)	82.33	(18.56)	-3.66	0.23	-9.7 to 2.4
social functioning	68.35	(21.04)	70.03	(24.05)	-1.68	0.63	-8.5 to 5.2
role - physical	53.01	(38.33)	56.98	(39.23)	-3.97	0.51	-15.7 to 7.8
role - emotional	57.43	(43.03)	55.03	(43.62)	2.40	0.72	-10.8 to 15.6
mental health	58.20	(18.23)	59.43	(18.97)	-1.23	0.67	-6.9 to 4.5
energy/fatigue	40.36	(17.17)	41.49	(19.15)	-1.13	0.69	-6.7 to 4.5
pain	53.55	(23.99)	58.14	(25.15)	-4.59	0.23	-12.1 to 2.9
general health	68.17	(19.00)	65.90	(19.34)	2.27	0.45	-3.6 to 8.1
Short form 36 - change in score (S.D.)							
physical functioning	3.73	(17.19)	5.00*	(18.97)	-1.27	0.65	-6.4 to 4.2
social functioning	3.94	(25.26)	10.59***	(26.52)	-6.65	0.10	-14.5 to 1.2
role - physical	12.95**	(44.58)	18.60***	(45.73)	-5.65	0.42	-19.4 to 8.1
role - emotional	11.25*	(45.17)	22.48***	(50.47)	-11.23	0.13	-25.8 to 3.3
mental health	7.17***	(19.20)	9.98***	(19.14)	-2.81	0.35	-8.7 to 3.1
energy/fatigue	10.06***	(19.57)	14.58***	(21.96)	-4.52	0.17	-11.0 to 2.0
pain	11.38***	(28.51)	12.34***	(27.20)	-0.96	0.82	-9.4 to 7.5
general health	-0.67	(13.90)	1.69	(18.83)	-0.97	0.36	-7.4 to 2.7

Follow-up statistical comparisons between trial groups are for change in score
Asterisks denote significant changes in score from the baseline (*p < 0.05, **p <0.01, ***p <0.001)

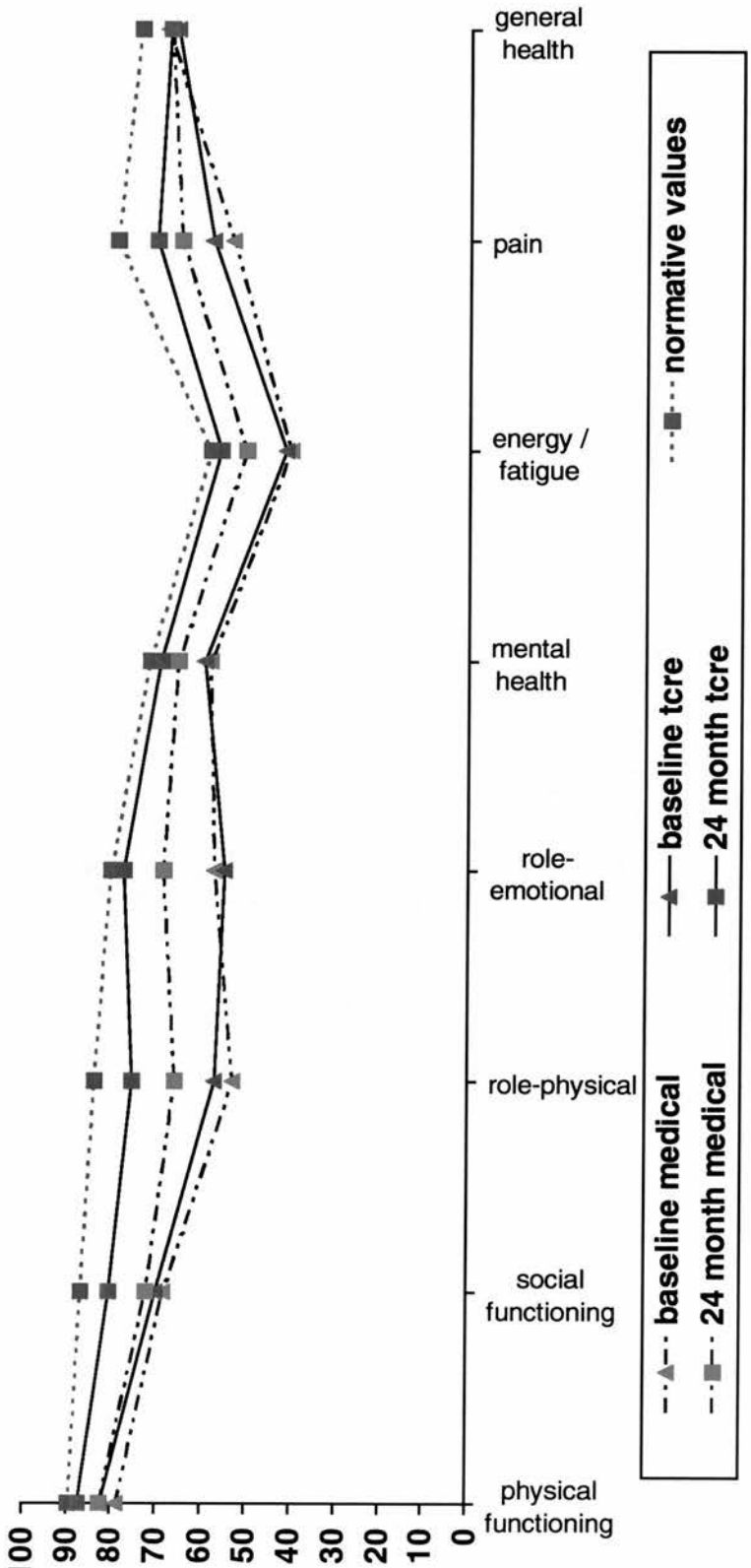


fig. 4.1. Short Form 36 scores

Chapter 5

A Randomised Controlled Trial Comparing Microwave Endometrial Ablation with Transcervical Resection of the Endometrium for Women with Heavy Menstrual Loss:

Patients, methods, operative details and clinical and quality of life outcomes at four months.

INTRODUCTION

Hysteroscopic endometrial destructive techniques are proven alternatives to hysterectomy for women with excessive menstrual loss without excessive uterine size or abnormality(55,105-107). The most commonly used techniques in the UK are laser ablation and combination resection rollerball(118,140). These procedures achieve high satisfaction rates, have quick recovery times and are safe(59,118). Complication rates determined through a large national audit are around 1%, with bleeding and perforation the most frequent problem which are more commonly encountered at resection rather than laser ablation(59). The main problem with these hysteroscopic techniques is that they are technically demanding, necessitating specialist training and equipment. In an effort to simplify endometrial destruction a number of alternatives to the hysteroscopic surgical techniques have evolved which claim to be easier to learn and use, but have similar clinical effectiveness, with increased safety(112,114,184). To date none of these new techniques have undergone rigorous comparison with TCRE or laser ablation in a randomised controlled trial.

One of these procedures, microwave endometrial ablation, has undergone testing equivalent to phase 1-3 for drug trials and the first series of treatments were reported in the Lancet in 1995(114). In this small study of 23 women an 83% success rates was achieved with single treatment, with 56% amenorrhoea, abolition of dysmenorrhoea in 95%, and very fast treatment times (1 - 2

minutes). Endometrial sampling was undertaken in all cases, followed by endometrial preparation with danazol, and peri-operative ultrasound to determine size, presence of fibroids and correct probe siting. There were no complications in any of the 78 women who had undergone MEA at that stage. These results were achieved in pre-selected women with normal sized uterii with regular endometrial cavities.

To properly evaluate MEA a randomised controlled trial was required comparing it with a proven hysteroscopic surgical technique. We obtained ethical committee approval to undertake a pragmatic(89,90) randomised controlled trial comparing microwave endometrial ablation with transcervical resection of the endometrium for women complaining of heavy menstrual loss. This trial was partially funded by Microsulis PLC, the manufacturers of the microwave equipment. Transcervical resection of the endometrium was chosen as the hysteroscopic technique as this was the personal preference of the surgeons undertaking the trial and also it is more likely that the equipment is available outwith specialist centres, unlike laser, which should increase the generalisability of the results.

AIMS

The aims of the study were to compare MEA™ with TCRE for women referred for or requesting endometrial ablative surgery as treatment for heavy menstrual loss. The following issues were addressed:

a. **Outcome in terms of effectiveness, operative details, recovery times and morbidity**. The principle outcome measure for this trial is short term satisfaction at four months, although follow-up will be continued through one and two years. The power study calculation is based on satisfaction rates which are known to be around 80% from previous randomised trials(105,106,118). Results of the other outcome measures are also well known for transcervical resection of the endometrium, although mean operating times from the earlier trials of 30 to 45 minutes(104-107) have been halved(131). It is thus essential to undertake a prospective randomised controlled trial of MEA with TCRE rather than compare MEA results obtained from previous trials evaluating TCRE. Data pertaining to MEA are restricted to the one small uncontrolled study mentioned in the above introduction(114), therefore most of these outcomes measures are being collected on it for the first time. As this is a new technique effects on bladder and bowel will be evaluated, to determine if any changes in symptoms occur to these local structures, following treatment by each technique. This was undertaken previously for TCRE(109,189), when no adverse effect on bladder or bowel symptoms was found.

b. **Changes in health related quality of life resulting from treatment of heavy menstrual loss with MEA compared with TCRE.** When treating a chronic, non life threatening condition such as heavy menstrual loss an important consideration should be the effect of treatment on the quality of life of the women. This area was identified as a deficiency of previous trials evaluating treatments for menorrhagia by the Effective Health Care group(51). It has been demonstrated that women suffering from heavy menstrual loss suffer significant reduction in all aspects of health related quality of life as measured by the short form 36(52). The validity and reliability of the SF-36 has been established for US (146,190,191) and UK(52,148,180) patient populations. Despite being a generic health questionnaire, there is also evidence for the instrument's validity, reliability and responsiveness to changes in health related quality of life for women with menorrhagia(53,171,182,192). One uncontrolled observational study showed that quality of life was improved following treatment for menorrhagia, with the greatest benefit following surgery(54). Several randomised controlled trials evaluating surgical treatments for menorrhagia have used SF-36 as a comparative outcome measure(83,105,108). These trials commenced before the normative values for that countries population were known, hence baseline measurement could not be made and so the most important measurement, change in health was not established. The only randomised controlled trials which have both baseline and follow-up SF-36 results for treatments for menorrhagia to date are contained in this thesis.

PATIENTS AND METHODS

Eligibility

Women were eligible for this study if they were pre-menopausal, were referred for and suitable for endometrial destructive surgery (as in Chapter 3) and willing to be randomised to either surgical technique.

Sample Size

Power study calculations based on rates of satisfaction with transcervical resection of the endometrium at four to six months of about 80%(105,106), determined that 230 women would yield an 80% chance of detecting a difference in satisfaction of 15%, which would be significant at the 5% level (InStat 2, GraphPad software).

Recruitment

Two hundred and sixty three women were recruited to the trial over 18 months between September 1996 and March 1998. Referrals for endometrial ablative surgery from nine of eleven consultants were assessed for eligibility. As this was a pragmatic study, pre-operative assessment by scan or hysteroscopy was not routinely undertaken. Clinical examination by bi-manual examination and endometrial biopsy were used to determine clinical eligibility. If eligible, women were given a standard information sheet describing the two surgical techniques, the principles of randomisation and the aims of the study

(Appendix 5.1). Informed consent was obtained from those eligible and willing to be randomised. Treatment allocation was ascertained by opening the next in line of a series of sealed, opaque, sequentially numbered envelopes which contained the treatment code as determined by computer generated random number tables. These were stratified in balanced blocks of twenty and randomisation was equal to both treatments.

Protocol

Eligible women were identified from those referred to the gynaecology out patient department for endometrial ablative surgery and after obtaining informed consent, women were randomised to either MEA or TCRE. Baseline clinical and health related quality of life measurements were determined by patient self completion of a clinical questionnaire and Short Form 36 (Appendix 1a) at recruitment. The clinical questionnaire was based on a validated menstrual questionnaire developed by the Health Services Research Unit in Aberdeen(182)(Appendix 5.2) Additional questions pertaining to bladder and bowel symptoms were also included. A subcutaneous injection of goserelin 3.6mg was given to all those recruited, and five weeks later they were admitted for operation.

All the operations were undertaken by two named operators, Dr K G Cooper and Dr C Bain, who were senior specialist registrars. Both were experienced hysteroscopic surgeons, and had attended one training session to learn

microwave ablation and had performed five MEA's each prior to the trial commencing. All procedures were performed under general anaesthesia and concomitant rectal analgesia using the non steroidal anti-inflammatory, diclofenac or if contra-indicated, paracetamol was administered. TCRE was undertaken using a diathermy resectoscope and glycine as described in the introductory chapter. Those allocated to MEA underwent ultrasound scan to determine endometrial thickness and carbon dioxide 5mm hysteroscopy to identify any fibroids and confirm placement in the endometrial cavity. Microwave ablation was then performed using the technique described in the introductory chapter. An operative questionnaire was completed at this time by the surgeon which determined operating times, complications, analgesia requirements and post-operative stay (Appendix 5.3). Analgesia post-operatively was oral or intramuscular opiate, according to the patients' wishes.

Follow-up was undertaken at a minimum of four months following the operation and consisted of a self completed questionnaire identical to that at recruitment with additional questions to determine satisfaction with, and acceptability of treatment and also bladder and bowel function (Appendix 5.4). After completing the questionnaire a consultation with a clinician was undertaken to answer questions and to remind the patient that postal questionnaires would be sent at one and two years post procedure.

Statistics

Data were entered onto a database created on SPSS for windows and all analyses were undertaken using this programme or by InStat version 2 (GraphPad software). Analysis was by 'intention to treat', that is women remained in the group to which they were originally allocated, irrespective of subsequent treatment received. Independent and paired t-tests were used for continuous variables (independent and related) with a normal distribution, and the Mann-Whitney U test for ordinal or non parametric continuous variables. The Chi-square or Fisher's Exact test were used for independent nominal data, and McNemar's and Wilcoxon's rank sum tests for paired nominal data describing dichotomous and related variables respectively.

RESULTS

Patient Characteristics

Two hundred and sixty three women were randomised, 129 to MEA and 134 to TCRE. Table 5.1 summarises the pre-operative details of the participants, and confirms the comparability of the groups at entry. Table 5.5 shows baseline quality of life scores, which again are comparable except for the pain component, which shows a significantly higher (better) score in the TCRE arm. 65% having MEA and 60% allocated TCRE described their periods as very heavy, with 60% in both arms having their problem for over three years. The sexual function of 56% and 51% respectively of these women was either

severely affected or prevented by excessive bleeding with just over 20% in each arm also complaining of dyspareunia. Bladder and bowel symptoms were also comparable at baseline for each group (table 5.4)

Operative data

The treatment actually received and the operative details are summarised in table 5.2. 8% of the MEA arm and 10% of the TCRE arm were sterilised at the time of the procedure and are not included in operating times. Four women in the MEA arm underwent TCRE as a result of failure of the microwave equipment. Operative times for the microwave, which were significantly quicker than TCRE, did not include the ultrasound examination (performed immediately pre-operatively), but did include the hysteroscopic assessment. The mean fluid absorption at TCRE was 318 mls, and no deficit over 1500 mls occurred. Blunt perforations with an inactive hysteroscope and microwave probe occurred once in each arm, which caused bleeding resulting in immediate hysterectomy in one case. A false passage was created during dilatation on one patient in the TCRE arm, necessitating abandoning the procedure to a later date. No damage occurred to any organ other than the uterus in any of the cases. Bleeding requiring the placement of an intra-uterine 14 gauge Foley catheter for six hours occurred in five women in the TCRE group. Post-operative bleeding occurred in three women who underwent TCRE which settled with conservative management. Re-admission was required for three women in the MEA arm with secondary haemorrhage which settled with conservative

management using antibiotics and for one woman with pain. Four women were re-admitted in the TCRE arm; two with pain and two to have repeat procedures. The majority of women felt that they had fully recovered within four weeks of their operation (72% of MEA, 66% of TCRE, p = 0.83).

It was noticed that when operating on women with submucous fibroids using the microwave, a marked drop in temperature occurs when the probe tip encounters the fibroid. With the probe maintained in the same position, a slow rise and return to optimal operating temperature is observed, following which the procedure can be completed.

Menstrual status at follow-up

Data are available for 145 women, 122 allocated MEA, and 123 to TCRE. The remaining 18 women have failed to attend their follow-up visit and postal questionnaires have been sent. Changes in bleeding, pain and related menstrual symptoms are summarised in table 5.3. Both techniques lead to highly significant, and equivalent reductions for all parameters relating to menstrual pain and bleeding. Transcervical resection of the endometrium achieved higher rates of amenorrhoea and fewer women who bled for more than seven days per cycle. New pelvic pain was reported by 6% in each arm, whilst dysmenorrhoea was highly significantly and equally reduced in both arms. Pre-menstrual symptoms were significantly reduced by both techniques, except for breast discomfort in the MEA arm, although no significant

differences were detected between the two procedures. Both MEA and TCRE lead to a highly significant reduction in work-days lost due to menstrual symptoms.

Table 5.4 summarises urinary and bowel symptoms reported by participating women at baseline and follow up. Rates of reported symptoms are similar for both surgical techniques at follow-up and unchanged from baseline for bowel symptoms, whereas urinary symptoms are generally reduced at four months.

Patient satisfaction

Patient satisfaction at four months is reported in table 5.5. Similar numbers in each arm were totally or generally satisfied with the outcome and around 90% in each arm found the treatment acceptable and would recommend it to a friend. Women who felt that they were cured or had an acceptable improvement in symptoms were also comparable following MEA or TCRE.

Health related quality of life

Table 5.6 and figure 5.1 show SF-36 scores at baseline and four month follow-up. Values at baseline are comparable in both cohorts except for the pain component of TCRE which has a higher (better) value. Scores are improved by both techniques for all eight health scales and significantly so for all eight following MEA and six following TCRE. Improvements are equivalent in both groups except for the pain scores which show significantly better improvement

following MEA. Figure 5.1 shows total baseline and follow-up scores in both arms compared with normative values for healthy women of equivalent age in the UK(148).

Sexual function was equally and significantly improved by both operations as were rates of dyspareunia (Wilcoxon's rank sum test, both $p< 0.001$). At baseline 5% of women in each arm could undertake leisure activities unaffected by their periods. Following treatment, this was significantly improved to 54% and 63% for MEA and TCRE respectively (Wilcoxon's rank sum test, both $p< 0.001$).

Effect of cavity size, fibroids and endometrial thickness on MEA results

These stratified analyses are summarised on table 5.7. Menstrual outcomes and rates of satisfaction with and acceptability of treatment are no different when cavity lengths of under 8cms are compared with those greater than 8cms in the MEA arm. The menstrual outcomes of women treated by MEA who had submucous fibroids of greater than 2 cms size were worse than those with normal cavities though not significantly so. Of those women who regarded their operation as unsuccessful at follow-up, the most prevalent feature common to this group was the presence of an endometrial thickness of greater than 4 mms measured by transvaginal ultrasound at operation. Women with a body weight of greater than 80 kg were just as satisfied as those lighter (78% v 73%, $p = 0.52$). Amenorrhoea rates were 16% for those over 80 kg and 31% in

women under this weight ($p < 0.33$), although mean bleeding scores were identical at 8.2.

DISCUSSION

This is the first randomised trial to evaluate a non hysteroscopic endometrial ablative technique. All of the operations were undertaken by two registrars who were experienced hysteroscopic surgeons, and who had undergone one training session for MEA and performed five cases each prior to the trial. The number of recruits, 263 women, easily satisfied the power study requirements and should allow for drop-outs over the two years over which follow-up is planned. Data on the missing eighteen subjects so far is being sought, though it is known from gynaecological records that none have been re-admitted for any reason. The only previous report of MEA(114), recruited women for operation with careful pre-operative assessment to ensure normal sized, regular cavities. This trial adopted a pragmatic(89,90) approach, and entry was based on a subjective complaint of intolerable menstrual loss. Also ultrasound and hysteroscopic assessment were not utilised unless clinical examination dictated, or an endometrial biopsy could not be obtained. This policy, which reflected normal clinical practice, sought to recruit a diverse population with "dysfunctional uterine bleeding." This lead to some women with larger cavities, and submucous fibroids being recruited, but should increase the generalisability of the results.

Operative details

An important factor regarding blind ablative techniques is that confirmation of correct placement in the uterine cavity is ensured. This is easily achieved with an ultrasound examination. In this study, gas hysteroscopy was undertaken to determine the presence of fibroids and establish their effect on outcome. An additional benefit of undertaking hysteroscopy was that subsequent placement of the microwave probe in the uterine cavity was ensured. Despite this additional procedure, MEA was significantly quicker than TCRE in both actual operating and total theatre time. In addition no irrigation fluid is required, although no problems were encountered with this in the TCRE arm (mean deficit 318 mls). Times for TCRE are significantly faster than reported in previous randomised controlled trials(105,106,109), but similar to more recent Aberdeen data(131). Technical failures with the equipment arose significantly more often in the MEA arm, necessitating four women having TCRE's instead. Conversion from TCRE to MEA was not undertaken as the efficiency of the microwave energy is compromised by the fluid milieu following initial glycine irrigation. This was the reason why gas rather than fluid hysteroscopy was used prior to performing MEA.

The perforation and hysterectomy rates in this trial were similar to previously reported National audit's and studies(59,103,105,118), though importantly none occurred with activated equipment and no damage resulted to any organ other than the uterus. All other operative parameters were similar in both arms and

all women received peri-operative antibiotic cover. Post-operatively analgesia requirements were low and equivalent with over 70% of women requiring no pain relief. Similar numbers felt that they had fully recovered within four weeks of their operation, although fewer than the 80% rate reported in a previous Aberdeen study(106).

The temperature drops noted when encountering a fibroid are likely to result from the increased blood flow in the fibroid creating a "heat sink" effect. This is compounded by the different properties and increased density of myomatous tissue when compared to endometrium.

Menstrual status

All parameters pertaining to menstrual blood loss were highly significantly and equally improved by both techniques. The exception to this were the lower amenorrhoea rates achieved with the microwave. Amenorrhoea is a useful benchmark as it is the only objective outcome measure available when menstrual blood loss is not formally measured. It should not be a principal determinant of treatment success however as ablative techniques should be offered to women who want lighter bleeding, as these women will be more satisfied than those desirous of amenorrhoea(163). The amenorrhoea rate for TCRE is comparable to that achieved at four month follow-up in the medical v. TCRE trial in Chapter 3, and by other recent randomised controlled trials(107), but higher than other randomised controlled trial and a national

audit(105,106,109,118). These rates, as with other outcome measures are lower than those achieved in some uncontrolled series reports(100,102), and specifically the only series describing MEA(114). This highlights the importance of randomisation and the need for caution when evaluating results of uncontrolled series reports. Results for women with larger cavities are reassuring, although menstrual results may not be quite as good if fibroids are present.

Dysmenorrhoea was markedly reduced by both procedures and new pain reported by a small proportion (6%) of women, once again dispelling previous reports of pelvic pain being a contraindication to endometrial destructive surgery. As in previous reports(106,109,181), associated peri-menstrual symptoms were significantly improved by both techniques, with TCRE leading to the largest changes. Whether this is purely achieved through a lessening of the anticipation of a heavy period, as has been suggested(161), or whether removal of an unknown endometrial product has occurred(193), still awaits full clarification.

Bowel symptoms at follow-up are unchanged, whereas urinary symptoms, including incontinence are improved following both ablative technique. Previous trials(109,189), have demonstrated little effect on urinary function following TCRE or laser ablation, so it is difficult to explain these improvements, especially the highly significant reduction in stress incontinence

following TCRE. What is more important is that MEA did not lead to any deterioration in bladder or bowel symptoms.

Satisfaction

Satisfaction with, and acceptability of treatment rates were high and comparable for both techniques, and remarkably similar to previous trials evaluating endometrial ablation(105-108) (including TCRE v. Medical treatment in chapter 3). These high levels of satisfaction are sustained for MEA even for women with larger cavities and with submucous fibroids.

Health related quality of life

Heavy menstrual loss is known to cause significant deterioration in general health and quality of life(52,171,185) which has often been overlooked in the evaluation of treatment in previous trials. This in part was due to the lack of a validated measurement tool that was sensitive to change, had been assessed in women with menstrual problems, and for which normative values for the healthy population were known. Short form 36 fulfils all of these criteria and hence its use in this study. The reduced SF-36 scores observed at baseline in this trial are reduced for all eight subscales from the mean normative values for women of equivalent age in the UK(148), and are comparable to previous studies involving women with heavy menstrual loss(52). The SF-36 recruitment scores from the study population in chapter 3 of this thesis, comparing TCRE with medical treatment, are similar except for a higher social functioning score.

The general health scale is least affected for these women with heavy menstrual loss. The significant difference at baseline in the pain subscale scores between the two groups is at odds with the menstrual pain scores (table 5.1).

Scores following MEA show improvement in six of the health scales to normative values, social functioning and pain, although being significantly improved from recruitment, remain below normal levels. Transcervical resection of the endometrium returned three of the health scales to normal, and significantly improved six of the eight variables. This is surprising when compared to the TCRE / medical trial in Chapter 3 where all SF-36 scores were returned to normative levels by TCRE at four months, although these were women who were not initially referred for surgical treatment. The differences in baseline scores of the pain subscale can be corrected for by using an analysis of co-variance (ANCOVA) test when comparing change in scores. When undertaken change in scores for this variable becomes 0.06 (from 0.03). Neither change in scores, nor final total scores are significantly different for any of the other SF-36 scales in the MEA and TCRE cohorts.

The differences between the SF-36 outcome results of the two trials undertaken in this thesis should indicate that caution should be used before comparing results of different study groups and questions the reliability of comparisons with a reference "normal" population from a different part of the country. Ideally normative reference data with range and mean values should be

available for each region. The SF-36 questionnaire is however sensitive to change over time for women with menstrual problems(52,53), and gives meaningful results which are amenable to statistical analysis when making comparisons of outcome for two or more treatments.

Sexual function and dyspareunia rates were similarly improved following both techniques, these effect has been previously reported(105,149), whilst there was also a highly increased ability to undertake leisure pursuits unaffected. The reduction in the number of days off work, lost through menstrual symptoms, is a major benefit of these techniques, as a substantial amount of money is lost annually because of this.

Conclusion

This trial has shown that microwave endometrial ablation has achieved satisfaction rates and improvements in menstrual symptoms comparable to transcervical resection of the endometrium. The results were not as good as obtained in an uncontrolled series report of MEA, but those women were pre-selected to have normal sized cavities and no fibroids. Importantly MEA led to highly significant improvements in all eight health scales of the quality of life questionnaire, short form 36. The advantages of MEA over TCRE are that the operative technique is very easy to learn, hysteroscopic surgical skills are not required, and it is safe for both operator and patient. The technique, even with concomitant hysteroscopy is significantly faster than TCRE.

A disadvantage of this and all other blind ablative techniques is the inability to evaluate the endometrial cavity and obtain an operative, pathological specimen. Although MEA, as with other ablative techniques, should never be undertaken without first excluding endometrial atypia, there are reports in the literature of endometrial carcinoma detected in resection specimens from TCRE despite previous negative endometrial biopsy(154,155). Long-term follow-up of these patients and investigation of any changes in bleeding patterns will be required to establish rates of subsequent neoplastic change and mode of presentation. After one year results are in fact similar to those at four months. Amenorrhoea rates are however 39% for both techniques, with hysterectomy rates of around 8%. Complete description of the results after one year can be found in the Lancet paper cited below

PUBLICATION

The above trial containing the one year results of "a randomised trial comparing microwave endometrial ablation with transcervical resection of the endometrium for women with heavy menstrual loss", will be published in the Lancet in November/December 1999.

Table 5.1 Baseline characteristics of each randomised group at recruitment. Values are numbers (percentages) of women unless stated otherwise

	Randomised M.E.A (n = 129)		Randomised T.C.R.E. (n = 134)	
Mean age (S.D.)	41.1	(6.7)	41.	(8.4)
Weight/kg (S.D.)	68.5	(14.0)	72.9	(17.4)
Menstrual symptoms				
irregular periods	66	(51)	76	(57)
3 - 7 days bleeding	58	(45)	54	(40)
>7 days bleeding	70	(54)	80	(60)
>3 days heavy bleeding	88	(69)	82	(64)
dysmenorrhoea	91	(72)	90	(68)
Sanitary protection required				
single	18	(14)	21	(16)
double or more	111	(86)	113	(84)
Bleeding score - mean -(S.D.)	28.5	(9.6)	28.0	(9.2)
Pain score - mean -(S.D.)	19.1	(11.4)	17.0	(12.5)
Premenstrual symptoms				
bloating	107	(87)	115	(87)
breast discomfort	94	(76)	1.3	(79)
irritability	104	(86)	117	(87)
headaches	88	(74)	93	(73)
depression	71	(62)	79	(61)
Work days lost due to menses				
none	13	(10)	20	(15)
none, but work suffers	54	(43)	52	(39)
one	14	(11)	12	(9)
two or more	46	(36)	49	(37)

Table 5. 2 Operative details for MEA and TCRE. Values are numbers (percentages) of women unless otherwise stated

	Randomised M.E.A (n = 129)		Randomised T.C.R.E. (n = 134)		95% C.I. for difference	P value
Mean cavity length in cms (S.D.)	7.4	(0.9)	7.5	(0.8)	-0.33 to 0.07	0.2
Submucous fibroids >2cms	14	(11)	18	(14)	-5 to 10%	0.1
Mean operating time in minutes (S.D.)	11.4	(10.5)	15.0	(7.2)	-5.7 to -1.4	0.001
Total theatre time in minutes (S.D.)	20.9	(11.3)	26.2	(8.7)	-7.7 to -2.8	< 0.001
Intra-operative problems						
abandoned procedure	5	(4)	5	(4)	-4 to 5%	0.57
equipment failure	11	(9)	3	(2)	1 to 12%	0.02
blunt perforation	1	(1)	1	(1)		
haemorrhage	0	(0)	5	(4)		
Treatment received						
MEA	124	(97)	1	(1)		
TCRE	4	(3)	129	(96)		
repeat TCRE	0	(0)	2	(1.5)		
Hysterectomy	1	(1)	2	(1.5)		
Post-operative analgesia						
none	90	(71)	99	(74)	-15 to 7%	0.48
oral	23	(18)	19	(14)		
injectable	14	(11)	16	(12)		
Mean post op stay in hours (S.D.)	13.4	(17.6)	16.7	(21.2)	-8.0 to 1.5	0.17
Re-admitted	4	(3)	7	(5)	-7 to 3%	0.17

95% C.I. for difference = 95% confidence intervals for difference in means or proportions(%).

Table 5.3 **Menstrual status and symptoms at four month follow-up. Values are numbers of women (percentages), unless stated.**

	Randomised M.E.A (n = 122)		Randomised T.C.R.E. (n = 123)		95% C.I. for difference	P value
Menstrual status						
unchanged or heavier	17	(14)	8	(7)	-0.1 to 15%	0.08
Duration of bleed						0.01
amenorrhoea	34	(27)	45	(37)	-20 to 2%	
1 - 3 days	21	(17)	11	(9)	0 to 17%	
3 - 7 days	51	(42)	62	(50)	-21 to 4%	
>7 days	17	(14)	5	(4)	2 to 16%	
sanitary protection required						
single	68***	(76)	59***	(76)	-12 to 14%	0.24
double or more	21	(24)	19	(24)		
>3 days heavy bleeding	13***	(11)	8***	(7)	-2 to 11%	0.43
Bleeding score - mean -(S.D.)	8.2***	(9.9)	6.4***	(6.4)	-4.8 to 1.7	0.36
Pain score - mean -(S.D.)	5.1***	(5.2)	4.3***	(4.3)	--1.1 to 5.0	0.22
Dysmenorrhoea - same or worse	15***	(12)	11***	(9)	-4 to 11%	0.68
Premenstrual symptoms						
breast discomfort	80	(66)	74**	(63)	-6 to 18%	0.58
bloating	90*	(75)	76***	(64)	0 to 23%	0.07
irritability	74***	(62)	83***	(70)	-19 to 5%	0.18
headaches	56***	(47)	63***	(53)	-18o 7%	0.38
depression	50**	(42)	45***	(39)	-8 to 17%	0.69
Work days lost due to menses						
none	60***	(67)	55***	(71)		
none, but work suffers	17***	(19)	11***	(14)		
one	4	(5)	4	(5)	-8 to 8%	0.85
two or more	8***	(9)	8***	(10)		

Asterisks denote changes from baseline (*p < 0.05, **p < 0.01, ***p < 0.001)
95% C.I. for difference = 95% confidence intervals for difference in means or proportions(%).

Table 5.4 Urinary and bowel symptoms at baseline and four months. Values are numbers of women (percentages) unless stated otherwise

	Randomised M.E.A (n = 122)		Randomised T.C.R.E. (n = 123)		95% C.I. for difference	P value
Urinary Symptoms at baseline						
frequency	48	(40)	47	(38)		
urgency	38	(32)	36	(28)		
nocturia	47	(40)	41	(33)		
urge incontinence	32	(29)	36	(29)		
stress incontinence	61	(50)	62	(47)		
Bowel symptoms at baseline						
constipation	25	(20)	28	(21)		
diarrhoea	11	(9)	5	(4)		
mixed	0	(0)	0	(0)		
Urinary symptoms at 4 months						
frequency	41	(34)	39	(32)	-10 to 14%	0.89
urgency	29	(24)	34	(28)	-15 to 7%	0.71
nocturia	36	(30)	31	(25)	-7 to 16%	0.14
urge incontinence	27	(22)	25	(20)	-8 to 12%	0.58
stress incontinence	50	(41)	42***	(34)	-5 to 19%	0.51
Bowel symptoms at 4 months						
constipation	23	(19)	28	(23)	-14 to 6%	0.36
diarrhoea	13	(11)	4	(3)	-1 to 14%	0.10
mixed	2	(2)	0	(0)	-1 to 4%	0.49

Asterisks denote significant changes from the baseline (*p < 0.05, **p <0.01, ***p <0.001)
95% C.I. for difference = 95% confidence intervals for difference in proportions(%)

Table 5.5 Patient satisfaction, effectiveness and acceptability of treatment, and recommended treatment at four months. Values are numbers of women (percentages) unless stated otherwise.

	Randomised M.E.A (n = 122)		Randomised T.C.R.E. (n = 123)		95% C.I. for difference	P value
Totally or generally satisfied with treatment	90	(74)	99	(81)	-17 to 4%	0.54
Cure or acceptable improvement in symptoms	90	(74)	95	(77)	-14 to 7%	0.66
Treatment acceptable	113	(92)	116	(94)	-18 to 5%	0.8
Would you recommend your treatment? yes	104	(86)	110	(89)	-13 to 4%	0.59

Asterisks denote significant changes from the baseline (*p < 0.05, **p <0.01, ***p <0.001)
95% C.I. for difference = 95% confidence intervals for difference in proportions(%)

Table 5.6 Short Form 36 Health Survey Questionnaire :- mean baseline scores and change in score at two-year follow up. Scores range from 0 → 100 (worst → best)

	MEA n = 122 mean	SD	TCRE n = 123 mean	SD	P value	95% C.I.
Short Form 36 - baseline scores (S.D.)						
physical functioning	82.86	(21.57)	81.69	(22.72)	0.67	
social functioning	59.34	(22.63)	59.61	(23.18)	0.92	
role - physical	56.40	(43.11)	63.52	(41.29)	0.17	
role - emotional	59.94	(42.98)	62.46	(42.60)	0.63	
mental health	62.79	(18.81)	63.25	(20.94)	0.85	
energy/fatigue	43.64	(22.28)	43.09	(24.25)	0.85	
pain	55.47	(28.31)	62.96	(25.75)	0.03	
general health	69.48	(21.98)	71.75	(20.07)	0.38	
Short form 36 - change in score (S.D.)						
physical functioning	5.75***	(19.25)	1.23	(21.78)	0.09	-0.7 to 9.8
social functioning	12.93***	(25.36)	8.38***	(24.17)	0.15	-1.7 to 10.8
role - physical	25.61***	(47.61)	15.65***	(42.27)	0.08	-1.4 to 21.3
role - emotional	19.94***	(44.67)	8.94*	(45.58)	0.06	-0.4 to 22.4
mental health	8.03***	(19.85)	7.17***	(22.39)	0.75	-4.5 to 6.2
energy/fatigue	16.44***	(23.08)	14.54***	(26.55)	0.55	-4.4 to 8.18
pain	15.3***	(40.99)	5.14	(30.15)	0.03	1.1 to 19.2
general health	6.30***	(20.59)	3.25*	(18.79)	0.23	-1.9 to 8.0

Asterisks denote significant changes from the baseline (*p < 0.05, **p <0.01, ***p <0.001)

Table 5.7 **MEA only; the effect of presence of submucous fibroids and cavity length on outcome. Numbers of women are in parenthesis.**

Microwave Ablation	Fibroids > 2 cms			Cavity size		
	yes (14)	no (108)	p	up to 8cms (15)	>8cms (107)	p
Satisfied	78%	73%	0.86	76%	72%	0.66
Treatment acceptable	86%	94%	0.31	94%	86%	0.31
Mean bleeding score	12.7	7.7	0.07	8.2	8.8	0.82
Amenorrhoea	14%	29%	0.08	27%	29%	0.64
> 3 heavy days	43%	29%	0.07	32%	42%	0.7

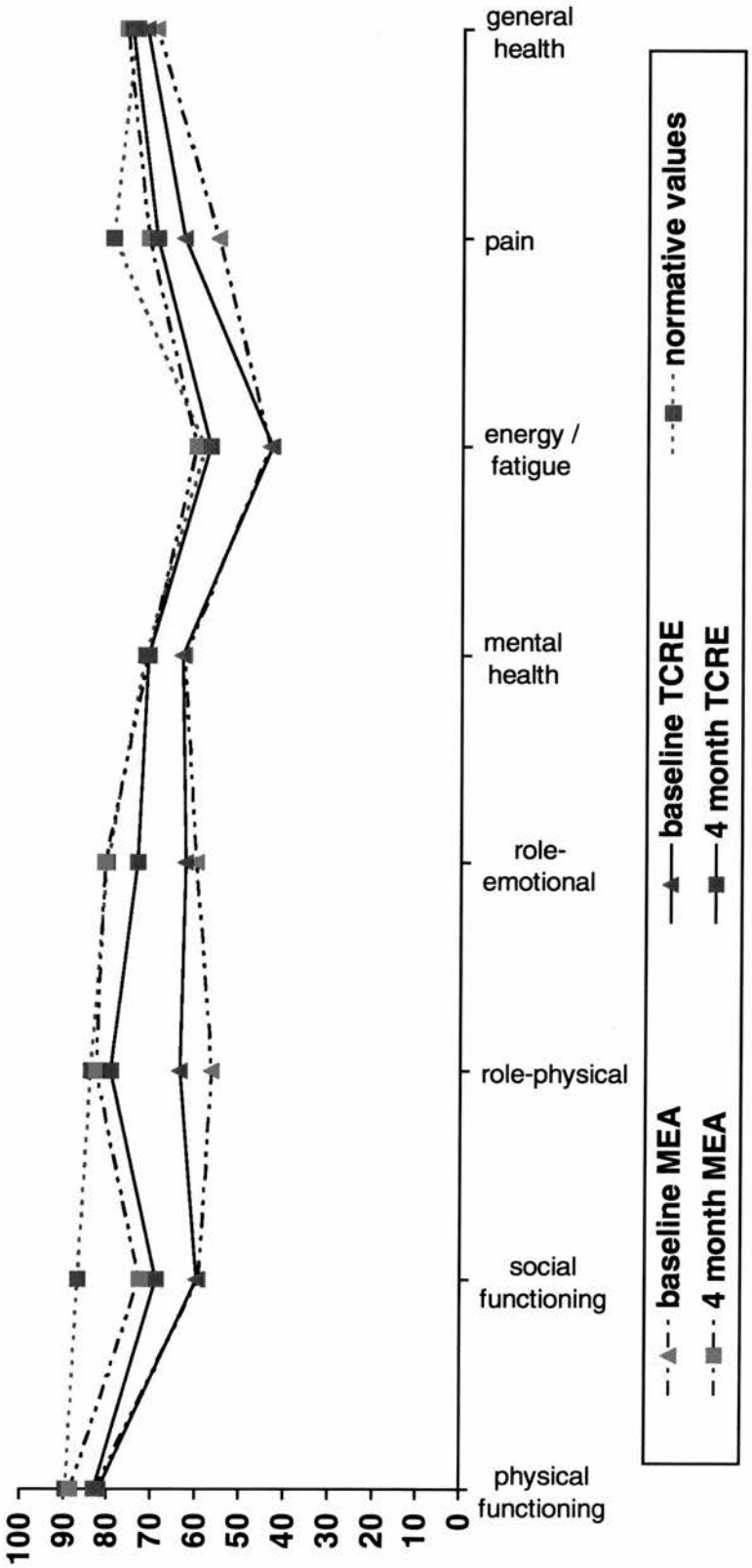


fig. 5.1. Short Form 36 scores

Chapter 6

Conclusions

a summary of the conclusions from the thesis
and recommendations for future research

Dysfunctional uterine bleeding exerts a significant burden on society. A large proportion of women presenting for treatment of heavy menstrual loss have monthly blood loss within the normal range, but still request help. Women complaining of heavy menstrual loss, "menorrhagia", make up 5% of all general practice patients, accounting for £7m of prescription charges(51) and up to 12% of new referrals to gynaecology clinics(47). There is considerable uncertainty about how best to treat these women and this is reflected by the variations in hysterectomy rates both nationally and internationally. Within five years of referral to a gynaecologist, up to 60% will have had a hysterectomy(49), and by the age of 55, 20% of women in the UK will have had a hysterectomy(50).

The statistics quoted above were gathered before the widespread implementation of endometrial destructive surgery. These endometrial ablative techniques were expected to reduce the hysterectomy rate, but may not have had the desired effect(138) and some suggest an increase in operative interventions. The figures in table 6.1, however, represent national data for all hysterectomies for menorrhagia and does not identify those that were suitable for ablation. Local data, from areas with good uptake of proven endometrial surgical techniques, are more appropriate for inspection and can demonstrate a reduction in benign hysterectomies for menorrhagia(194). National data may be further confused by a preference towards hysterectomy amongst senior gynaecologists as the surgical procedure for menorrhagia(195), which may skew audit results by affecting uptake of endometrial surgery in eligible women. Finally, the availability of these less invasive techniques may also have attracted women for

surgical treatment who would not have considered a hysterectomy, hence the increasing numbers, although the possibility that treatment thresholds have lowered cannot be discounted. There is now good long-term data which suggests that hysteroscopic surgery is an acceptable alternative to hysterectomy and can replace it for the majority of women with dysfunctional uterine bleeding(107,151).

Endometrial surgery has been promoted as an alternative to hysterectomy, to be used once medical treatment has failed. Whilst this may be desirable it may not be an entirely appropriate statement. The correct place of these ablative techniques in the treatment armamentarium has yet to be established and can only be so once a combination of factors are known. Epidemiological data, preference and outcome expectations need to be ascertained, as do effect on health related quality of life. It is known that heavy menstrual loss has a significant impact on health related quality of life and this has been identified as an essential component of treatment outcome(51,91). Finally randomised trials with appropriate outcome measures are required comparing these techniques with non surgical managements of menorrhagia, and with ablative techniques themselves.

This work undertaken in this thesis has attempted to address some of these deficits in our knowledge. It has outlined the patterns of referral for women with heavy menstrual loss and established local epidemiological features including, preference, expectations and variations in health related quality of life. Present medical therapy was compared with transcervical resection of the endometrium in the context of a

randomised controlled trial, with both short and medium term results. Finally the first randomised controlled trial comparing a "new generation" endometrial ablative technique with transcervical resection of the endometrium was made. Operative and short term outcomes of this trial comparing microwave endometrial ablation with transcervical resection of the endometrium were presented. These two randomised controlled trials and the epidemiological data should help clarify the role of endometrial destructive surgery in the management of women with heavy menstrual loss. This concluding chapter aims to summarise these results and to make recommendations for the effective and efficient use of ablative surgery. Future trends in endometrial surgery are discussed and areas for future research identified.

The opening chapter provided an overview of our present understanding of menorrhagia, from aetiology and epidemiology to available treatments. Chapter 2 describes a survey of women complaining of heavy menstrual loss who were referred to the gynaecologist for the first time. The aims were to obtain socio-demographic data, epidemiological features, patterns of G.P. referral and treatment, treatment preferences and expectations, and effect of menorrhagia on health related quality of life. Whilst these aims were generally achieved, some of the methods and questions used could be improved upon if the survey were repeated. A standardised tool for measuring social class would be a useful addition, as would a questionnaire to the referring general practitioner outlining reasons for referral and expectations.

The generic health questionnaire, short form 36 is quite cumbersome both to complete, collect and analyse. It has wide ranging mean values and standard deviations for the population of women in the studies undertaken in this thesis. This can make interpretation of between and intra group results difficult as without normative reference values for the population under investigation, the actual item scores attained can have little meaning. Acceptable alternatives are not easily found. The Nottingham health profile(196), whilst quick to complete has not been evaluated for menorrhagia and is not as sensitive to change as SF-36(197). EuroQol suffers from similar problems(198), does not have normative values and has not been as widely evaluated or utilised as SF-36 for women with heavy menstrual loss. Short form 36, despite its deficiencies has been shown to be acceptable, sensitive and valid for baseline measurement of and change in health for women with menstrual problems(54,171,197), including women from Grampian(52,53). The shortened version short form-12 may prove easier to complete and collect, but awaits full evaluation. An alternative might be to use a condition specific questionnaire, as introduced in the Chapter 5(182), although this was itself compared with SF-36 and meaningful reference values are not available as it has only been administered to a relatively small population.

The results obtained for the socio-demographic and epidemiological data for Grampian differed from that obtained from the large Oxford studies. Care must of course be taken when comparing these populations which, although both from the UK, may have fundamentally different characteristics. A lower proportion of out patient referrals in Grampian were for heavy menstrual loss (6% v 15%). This may represent

different referral patterns from primary care as fewer (21%) in this region had been referred within one year of consultation and more (80% v 55%) had received medical treatment before referral. Also the Grampian figures may be lower as only women who were first time referrals with heavy periods, who had normal pelvic findings, and who were not requesting a hysterectomy were counted, as opposed to all-comers with heavy menstrual loss. A high proportion of women (64%) are disabled for more than two days per cycle, despite the aforementioned treatment rates in primary care. These statistics have enormous resource implications through work days lost and possibly ineffective prescribing, making the initiation of effective and acceptable treatment at primary care level a priority.

Rates of preference for a medical or surgical treatment were 30% which is slightly lower than other reported data. More surprising is that equal numbers exhibited preferences for either medical or surgical treatment. These women differed from each other in many ways, essentially those preferring medical treatment were less severely affected by there complaint and had it for a shorter length of time. Those preferring surgical treatment had all received medical treatment before, were less well educated as a group, and had greater desires for amenorrhoea. The traits of women who had no strong treatment preference tended to fall between the two preference groups.

Women referred for the first time with heavy periods have mean health related quality of life scores significantly lower than normative levels. Women with a strong preference for medical treatment have SF-36 scores that are near normal and have little

scope for improvement irrespective of type of treatment. It would be sensible to concur with their wishes, or if necessary demonstrate that no treatment is required so that any medical interventions with increased morbidity, which may not afford them tangible, benefit are avoided. Those with a surgical, or no preference were equally debilitated by their heavy periods with respect to quality of life.

It must be again stated that the socio-demographic and indeed short form 36 data obtained for the women of Aberdeen who participated in the studies may not be representative of women with similar complaints from other parts of the UK. Ideally, population data should be available, and used, which is representative of the geographical catchment area under investigation, although this is often not possible. The results obtained from the survey in this thesis can however serve as a reference for future Aberdeen studies on women with excessive menstrual loss.

Chapters 3 and 4 described a randomised comparison of transcervical resection of the endometrium with traditional medical treatments for women first referred to a gynaecologist with heavy menstrual loss. The aims here were to establish the role of endometrial ablation in the management of this condition. Outcomes were determined by measuring at four months and two years, patient satisfaction and acceptability of treatment, changes to menstrual status, changes to health related quality of life and additional treatments required. Whilst these aims have been satisfactorily achieved there are a number of different ways in which this study could have been undertaken or improved.

The menstrual scoring system used in the trials in this thesis was inherited from previous trials assessing TCRE in Aberdeen (106,109). They are effective in demonstrating change of score and for comparing treatments, but the scores themselves do not inform the reader of the actual level of blood loss. They have also not been adequately validated for the population under investigation. Pictorial blood loss assessment charts(34), which have high sensitivity and specificity when compared to objective menstrual blood loss measurement, would have been a useful addition to this study. It would have informed us of the actual incidence of true menorrhagia, the range of loss, and perhaps allowed more meaningful comparisons to be made. One drawback however is that sanitary pads and tampons have changed markedly over the last ten years and the chart system may require re-validation. An alternative would be to use the technique described by Gannon which has been validated and assessed for women undergoing ablative surgery (157).

The initial follow-up of four months may have been too short. Women who agreed to randomisation and were allocated medical treatment could have realised that the ability to have a TCRE existed after quite a short time. This could be viewed as a "hedging" option whereby if medical treatment was good, surgery was avoided, but if not, then TCRE could be requested after a relatively short time. Secondly, it is recognised that the full effect of ablative surgery may not become apparent until at least six months post operatively. Results at four months may therefore have underestimated the effect of TCRE. If a similar trial was to be undertaken initial follow-up should be at least six months after entry.

The criteria for eligibility for entry into the trial could also be regarded as controversial. In order to maximise recruitment, given the recruitment time limit of one year, and to remain as close to standard practice as possible it was decided to include all first time referrals complaining of heavy menstrual loss irrespective of number of previous medical treatments. It could be argued that it was wrong to offer more medical treatment to a woman who may have had two different treatments from her GP, or conversely, offer a TCRE to a woman who had no prior medical treatment. We felt that this was countered by allowing those women with a strong treatment preference to declare themselves, therefore if a woman conceded to randomisation then she was truly ambivalent to the treatment allocation. Secondly it was important that women who had varying degrees of medical treatment were recruited as we were attempting to establish the place of ablative surgery in the management of menorrhagia. This was previously thought to be once a trial of medical treatment had failed. It would have been interesting to have limited the study to those who had no previous treatment although this would not have been pragmatic and would have increased recruitment time to almost five years.

Criticism could also be made as to the actual medications prescribed. Some would argue that one predetermined optimal treatment should have been used. This was deemed inappropriate as it would naturally exclude referred patients that had already had this, therefore increasing recruitment time. Also this was not in keeping with the pragmatic nature of the trial which was to test a policy of medical treatment, not a specific medication. No patient received a treatment which had been shown to be

ineffective in the management of menorrhagia. The absence however of the Mirena intrauterine system does detract from the external validity of the results but it was not licensed at the time of the trial for the treatment of menorrhagia. This treatment merits a large comparative trial with an ablative technique in the future.

The outcomes at four months of the pragmatic randomised trial comparing medical treatment with TCRE were described in chapter 3. This revealed that women allocated to have TCRE were more likely to be totally or generally satisfied (76% versus 27%, $p<0.001$), to find the treatment acceptable (93% versus 36%, $p<0.001$), and willing to have the treatment again (93% versus 31%, $p<0.001$). Although pain and bleeding were significantly reduced by medical treatment the effect was modest in comparison to transcervical resection ($p<0.001$). Haemoglobin levels were significantly increased only following TCRE, although mean baseline levels were already within normal limits. Short form 36 scores were improved in both arms, although only transcervical resection returned them to normative values.

Medical treatment was less effective than transcervical resection of the endometrium, irrespective of previous treatment or type of medical management received. Early hysteroscopic endometrial surgery should therefore be considered by woman as initial gynaecological treatment of their heavy menstrual loss. The treatment choice should be made by the woman after a full discussion of the advantages and disadvantages of all the available options.

The results after two years consolidate the findings at four months, and also informs us of the surgical outcomes of those who refused initial randomisation because of a treatment preference. Women allocated medical treatment were significantly less likely to be totally or generally satisfied (57% v 79%, p = 0.002), to find their management acceptable (77% v 93%, p = 0.004), or to recommend their allocated treatment (24% v 78%, p< 0.001). 59% of women in the medical cohort had undergone TCRE, hysterectomy or both, whereas 17% in the TCRE cohort had undergone further surgery. Bleeding and pain scores were similar in the groups and highly significantly better than at recruitment. Short form-36 health survey scores were significantly improved from baseline for five of the eight health scores in the medical arm, and seven in the TCRE arm.

Early recourse to hysteroscopic surgery will afford women with dysfunctional uterine bleeding better relief of symptoms and improvements in health related quality of life. Reassuringly, over 80% of those managed by TCRE at the outset have avoided further surgical treatment and the hysterectomy rate at two years in this group was less than for those randomised to medical therapy (11% v 14%). This finding is particularly important as there was concern that the introduction of ablative surgery might lead to an increase in hysterectomy rates. The present recommendations stating that hysteroscopic endometrial surgery should be offered once medical treatment has failed cannot be upheld by these findings. An effective endometrial ablative technique should be one of a selection of treatments offered to all women who have completed

their family, with a diagnosis of dysfunctional uterine bleeding, irrespective of what treatment, if any, she received in primary care.

The second generation endometrial ablative technique, microwave endometrial ablation was compared in a randomised trial with transcervical resection of the endometrium and is described in chapter 5. The aims of the trial were to establish the effectiveness of MEA in terms of patient satisfaction with, and acceptability of the procedure, changes in menstrual symptoms, changes to health related quality of life, operative data and recovery times. These aims were achieved although some improvements could be made if a similar trial was undertaken in the future. Prototype equipment, such as our first microwave generator, is prone to breakdown which unless large numbers of recruits are involved can significantly effect results. Comparative trials should only commence once the final commercial model is available. In view of the geography of Grampian region, post operative stay was often dependent on the time of day that the operation took place. Ideally morning lists should be used to determine recovery and discharge times accurately. Again four month follow-up was used which is undoubtedly too early to assess menstrual outcomes properly. Six months should be the first assessment of treatment outcome, if not one year. Follow-up should continue ideally for at least five years to monitor outcome and longer still to ensure no longer term deleterious events.

Microwave ablation was shown to be a significantly faster technique than TCRE (11.4 v 15 minutes, $p = 0.001$). Post operative stay was less following MEA, though not

significantly so, whereas analgesia requirements were low and equivalent for both techniques(< 30%). Troublesome bleeding occurred in five cases of transcervical resection of the endometrium and no microwave cases. Technical difficulties arose more frequently with the microwave equipment (9% v 2%, p = 0.02), but may have been a result of the prototype equipment available for the trial. Satisfaction with treatment rates were lower following microwave endometrial ablation but not significantly so (74% v. 81%), whilst acceptability of treatment (92% v 94%) were equivalent. Health related quality of life was highly significantly improved following microwave ablation and less so by transcervical resection of the endometrium.

Both microwave endometrial ablation and transcervical resection of the endometrium achieve high satisfaction and acceptability rates and both have improved quality of life at four months. Microwave ablation is quick to perform, has low rates of morbidity and is a simple technique to learn and use. In the short term microwave endometrial ablation is a suitable alternative to transcervical resection of the endometrium, particularly for those unable to attain or maintain advanced hysteroscopic surgical skills. Longer term follow-up results are awaited from this trial at one, two and five years before its true worth is known.

Overall the aims of the work undertaken in this thesis have been achieved and some important findings have been made. These have been published as full original articles in peer reviewed journals, as referenced at the end of each chapter, and contained at the end of the thesis. One notable deficiency of the clinical trial work is the absence of

a health economic evaluation of the treatment regimens under investigation. This should form an integral part of any clinical evaluation nowadays, but funding was unfortunately not available for a health economist at the time of the work. Despite this the following paragraphs outline the most salient points of the thesis.

The incidence of gynaecological referral for women with heavy menstrual loss is about 8% for women in Grampian, which is lower than reported for other regions of the UK. Disappointingly, one fifth of those referred have not been prescribed treatment in primary care. As a population these women suffer from significantly reduced levels of health related quality of life as assessed using Short Form 36. Levels of treatment preference for medical or surgical treatment were equivalent and made up 30% of all the women referred to a gynaecologist with menorrhagia. Women with a strong preference for medical treatment were less severely compromised by their periods compared to women with no treatment preference or a surgical preference.

Medical treatment as prescribed by the gynaecologist achieved low levels of satisfaction, and acceptability when compared to TCRE. Similarly, menstrual symptoms were significantly more improved following TCRE, as were all components of health related quality of life. These results improved after two years for the medical arm, although they remained significantly poorer than the TCRE cohort, although by this stage almost 60% of those in the medical cohort had undergone TCRE, hysterectomy or both. Hysterectomy rates after two years were lower in the TCRE group than in the medical group(11 v. 14%). Women with a preference for TCRE had

higher hysterectomy rates, whilst those preferring medical treatment had loe surgery rates and no hysterectomies. The present recommendations for TCRE to be offered as treatment following a failed trial of medication cannot be upheld by these findings.

Microwave endometrial ablation was compared to TCRE in a randomised trial and was demonstrated to be faster to undertake and yet is safe and easy to learn. Outcomes, in terms of satisfaction, acceptability, menstrual symptoms and health related quality of life are comparable for the two techniques. It is important that hysteroscopy is undertaken prior to MEA™ to confirm presence in the uterine cavity. MEA™ is also capable of treating large and fibroid cavities. Results at one year reveal hysterectomy rates of around 8% for both MEA™ and TCRE.

THE FUTURE

Hysteroscopic surgical techniques have undergone more rigorous assessment in randomised trials than any other surgical technique. Long term results are now available and confirm the worth of these techniques. Table 6.2 confirms that the benign hysterectomy rate for menstrual disorders has been reduced from over 600 to less than 500 a year in Aberdeen since the introduction of endometrial surgery. Unfortunately uptake has been hesitant except in a few centres in the UK. This may represent a healthy scepticism and need to examine the results of these trials, before adopting these new procedures, but the surgical skills and training involved may also have put people off.

The new generation ablative techniques, such as microwave, thermal balloon and others have been introduced to simplify endometrial ablation, but these techniques require strict evaluation. They undoubtedly are fast, less morbid techniques, that are easy to learn and have the potential to be undertaken in the out-patient setting. Unfortunately, like transcervical resection of the endometrium, none at present can guarantee amenorrhoea whilst the long-term sequelae are yet to be fully explored. Technical improvements hold the key to there future success. Decreasing instrument diameters to reduce cervical manipulation will increase there acceptability in the out-patient setting. A prototype microwave probe is presently undergoing testing which is 5.5 mm diameter. Ensuring total endometrial destruction whilst maintaining strict energy safety levels remains the ultimate quest, and whilst this can occasionally be

achieved in a well prepared small regular cavity, it ideally should work on unprepared and irregular cavities. Once these newer ablative techniques become available it opens up the possibility of a definitive one stop investigate and treat, menstrual clinic in the out-patient setting.

Safe and acceptable non surgical techniques which are effective in the long-term would obviously be a major breakthrough in the management of menorrhagia. Unfortunately no drugs have been appropriately assessed over an adequate length of time or indeed in a pragmatic manner. The levonorgestrel intrauterine system offers the best immediate non-surgical alternative, with the obvious advantage of maintenance of fertility. Although it has been subjected to randomised controlled trials which show its potential, uptake and continuation rates need to be determined. The future however will probably see the emergence of totally new medical therapeutic concepts, such as targeted immunological destruction of the endometrial glands using monoclonal antibodies, photo-coagulative endometrial destruction which is undergoing investigative work already, or even gene therapy.

The impact of introducing ever new techniques seems to increase the number of procedures that are undertaken for menstrual dysfunction. Is this due to a lowering of the treatment threshold, or have women become less tolerant of menstruation? There is no evidence that the incidence of true menorrhagia has changed over the last fifty years, although as family sizes decrease the number of periods experienced by individual women are greater. Women have also become more informed of what is

available and what is and is not perceived to be acceptable, through increased media coverage of women's issues. This may have created a degree of "menstrual intolerance" in developed countries which is driving up demands for effective treatment modalities. If a safe, cheap out-patient treatment becomes available which can guarantee amenorrhoea, will we witness an explosion of "cosmetic" endometrial destruction?

The opposite approach is to investigate strategies to de-medicalise menstruation through effective education and counselling of those with normal menstrual loss with perceived menorrhagia. The difficulties here are many. Firstly, an effective and acceptable method for measuring total menstrual blood loss needs be developed. Also menstrual loss needs to be averaged out over a number of periods. Repeat testing is required if on successful counselling, a perceived increase in menstrual severity is subsequently reported. These along with maintaining a supply of trained and available menstrual counsellors potentially make this a prohibitively expensive and unacceptable option. Finally, this approach ignores the effect on quality of life that even perceived menorrhagia can have on women. Despite these drawbacks this technique deserves investigation as it represents the ultimate conservative treatment, although it might not be without associated morbidity. A trial exploring some of these ideas is underway in Oxford.

AREAS FOR FUTURE RESEARCH

- to develop effective and acceptable ways of measuring menstrual loss
- exploring methods of patient education to impart information in an effective, understandable and efficient way, in an effort to reduce treatment rates
- to assess the effect of lifestyle alteration e.g. diet and exercise on menstrual loss
- determining local epidemiological data to investigate the effect of the introduction of management protocols, including continuous audit.
- investigation of genetic aetiological factors with a possible view to treatment in the future
- identification, development and assessment of effective drug therapies
- rigorous evaluation of the most promising treatments in order to identify effective options for the women with heavy menstrual loss
- investigation and development of alternative therapies specifically targeting the endometrium, e.g. immunilogical.
- Assessment of the surgical treatment of heavy menstrual loss in the out-patient setting.

CONCLUSION

The demand for treatment of menstrual dysfunction is increasing. For the time being the condition remains a subjective assessment of the severity of menstrual loss and the known effect it has on the women's quality of life. Epidemiological data on menstrual dysfunction and its treatment varies from region to region, but suggests a need for implementation of management guidelines at primary care and secondary care levels. These guidelines will require a rolling audit programme with appropriate unbiased upgrading, to successfully rationalise care. Hysterectomy rates in the UK, whilst relatively low when compared to other Western countries, are still rising and there is a need to reduce them as the vast majority of uteri have no demonstrable pathology. Hysteroscopic surgical techniques can lower hysterectomy rates and are widely available, but have not been widely utilised.

Transcervical resection of the endometrium is, in addition, an effective and acceptable first line treatment for women attending the gynaecologist with heavy menstrual loss. It should not be withheld in suitable women in an effort to pursue medical therapy. Endometrial destructive techniques have the ability to return health related quality of life to normative levels, which, along with the prevention of anaemia, remains the ultimate treatment goal. Whilst these endometrial techniques undergo refinement to simplify them we must be vigilant to maintain their safety and effectiveness through continuing scrutiny in well constructed trials. The very long-term sequelae of all of these endometrial surgical procedures is unknown and particularly with the blind

ablative techniques utilising different types of energy, it is important to follow-up those treated to ascertain subsequent rates of gynaecological malignancy.

Women seeking treatment for their heavy menstrual loss should be provided with appropriate information and investigation of their complaint based on the best available evidence. Treatment, whether reassurance and counselling, medical or surgical, should likewise be evidence based. The final treatment choice should however be made by the women after full and informed consideration of the pros and cons of all the available therapeutic options. In the meantime researchers should strive to improve the investigative and treatment armamentarium of menstrual dysfunction in an effort to reduce the morbidity associated with the condition itself and also of the available treatment options.

Table 6.1 Hospital statistics for benign hysterectomy and endometrial ablation in England

Year ending	**1990**	**1991**	**1992**	**1993**	**1994**
Hysterectomy	73280	70675	71630	73169	73517
Endometrial ablation	1699	4224	7878	9982	9945
total	74979	74899	79508	83151	83462

Source:-

Hospital Episode Statistics Volume 1: Finished Consultant Episodes by diagnosis, operation and speciality.

Table 6.2 Hospital statistics for the surgical management of menorrhagia in Aberdeen

	1990	1991	1992	1993	1994	1995	1996	1997
Benign hysterectomy - any route	605	680	620	622	537	560	456	480
Endometrial ablation	44	116	118	164	290	364	315	307
total	649	796	738	786	827	924	771	787

Source:-

Information management and technology. Patient administration system. Aberdeen Royal Hospitals NHS Trust, 1998.

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Appendices

Appendix 1a Short Form 36

The following questions ask for your views regarding your health and how you feel about life in general. Answer all the questions, if you are unsure then think about your overall health and give the best answer you can.

1/ In general, would you say your health is ?

	(circle one)
excellent.....	1
very good.....	2
good.....	3
fair	4
poor	5

2/ Compared to four months ago, how would you rate your general health now ?

	(circle one)
much better.....	1
somewhat better.....	2
about the same	3
somewhat worse	4
much worse	5

3/ The following questions are about activities you might do during a typical day. Does your health limit you in these activities ? If so, how much ?

(circle one number for each question)

ACTIVITIES	YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a/ vigorous activities, such as running, lifting heavy objects or strenuous sports ?	1	2	3
b/ moderate activities such as moving a table, hoovering ,bowling or golf ?	1	2	3
c/ lifting or carrying groceries ?	1	2	3
d/ climbing several flights of stairs ?	1	2	3
e/ climbing one flight of stairs ?	1	2	3
f/ bending, kneeling or stooping ?	1	2	3
g/ walking more than a mile ?	1	2	3
h/ walking half a mile ?	1	2	3

I/ walking 100 yards	1	2	3
j/ bathing or dressing yourself	1	2	3

4/ During the past 4 weeks , have you had any of the following problems with your work or other regular daily activities as a result of your physical health ?

(circle one number for each question)

	YES	NO
a/ cut down on the amount of time you spent on work or other activities ?	1	2
b/ accomplished less than you would have liked ?	1	2
c/ were limited in the kind of work or activities ?	1	2
d/ had difficulty performing the work or other activities (e.g. it took extra effort)?	1	2

5/ During the past 4 weeks , have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	YES	NO
a/ cut down on the amount of time you spent on work or other activities ?	1	2
b/ accomplished less than you would have liked ?	1	2
c/ didn't do work or other activities as carefully as usual ?	1	2

6/ During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with friends, family or groups ?

(circle one)

not at all	1
slightly	2
moderately	3
quite a bit	4
extremely	5

7/ How much bodily pain have you had in the past 4 weeks ? (circle one)

none	1
very mild	2
mild	3
moderate	4
severe	5
very severe	6

8/ During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework) ? (circle one)

not at all	1
a little bit	2
moderately	3
quite a bit	4
extremely	5

9/ These questions are about how you feel and how things have been with you during the past 4 weeks.
For each question, please give the one answer that comes closest to the way you have been feeling. :- .....

(circle one number for each question)

HOW MUCH TIME IN THE LAST 4 WEEKS	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a/ did you feel full of life ?	1	2	3	4	5	6
b/ have you been nervous ?	1	2	3	4	5	6
c/ have you felt so down in the dumps that nothing could cheer you up ?	1	2	3	4	5	6
d/ have you felt calm and peaceful ?	1	2	3	4	5	6
e/ did you have a lot of energy ?	1	2	3	4	5	6
f/ have you felt downhearted and low ?	1	2	3	4	5	6

g/ did you feel worn out ?	1	2	3	4	5	6
h/ have you been happy ?	1	2	3	4	5	6
I/ did you feel tired ?	1	2	3	4	5	6

10/ During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives ,etc.) ?

(circle one)

all of the time 1

most of the time. 2

some of the time 3

a little of the time 4

none of the time.... 5

11/ How TRUE or FALSE is <u>each</u> of the following statements for you

(circle one number for each question)

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
a/ I seem to get ill more easily than other people	1	2	3	4	5
b/ I am as healthy as anybody I know	1	2	3	4	5
c/ I expect my health to get worse	1	2	3	4	5
d/ My health is excellent	1	2	3	4	5

Appendix 1b

Hospital Anxiety and Depression Scale

tick one box for each question

I feel tense or wound up

most of the time	0
a lot of the time	1
occasionally	2
not at all	3

I still enjoy the things I used to

definitely not as much	3
not quite as much	2
only a little	1
hardly at all	0

I get a sort of frightened feeling as if something awful is about to happen

very definitely, and quite badly	0
yes, but not to badly	1
a little, but it does'nt worry me	2
not at all	3

I can laugh and see the funny side of things

as much as I always could	3
not quite so much now	2
definitely not as much now	1
not at all	0

Worrying thoughts go through my mind

a great deal of the time	0
a lot of the time	1
from time to time, but not too often	2
only occasionally	3

I feel cheerful

not at all	3
not often	2
sometimes	1
most of the time	0

I can sit at ease and feel relaxed

definitely	0
usually	1
not often	2
not at all	3

I feel as if I'm slowed down

nearly all the time	0
very often	1
sometimes	2
not at all	3

I get a sort of frightened feeling like butterflies in my stomach

not at all	3
occasionally	2
quite often	1
very often	0

I have lost interest in my appearance

definitely	0
I donut take as much care as I should	1
I may not take quite as much care	2
I take just as much care as ever	3

I feel restless as if I have to be on the move

very much indeed	3
quite a lot	2
not very much	1
not at all	0

I look forward with enjoyment to things

as much as I ever did	0
rather less than I used to	1
definitely less than I used to	2
hardly at all	3

I get sudden feelings of panic

very often	3
quite often	2
not very often	1
hardly at all	0

I can enjoy a good book or TV programme

often	0
sometimes	1
not often	2
very seldom	3

Appendix 1c

Semantic Differential Technique

The following questionnaire involves marking a score on a scale between two opposite words (e.g. good and bad) to find out what you felt about the procedure you have just had. The words represent different ways you may feel about the procedure. If you think that a pair of words are not relevant, or it is neither one nor the other, then mark the central '0' rather than missing it out. Put one circle around your score on each line

e.g. if you thought the procedure was slightly unpleasant you might circle the number 1 in that line

painless	-3	-2	-1	0	1	2	3	painful
happy	-3	-2	-1	0	1	2	3	sad
good	-3	-2	-1	0	1	2	3	bad
pleasant	-3	-2	-1	0	1	2	3	unpleasant
positive	-3	-2	-1	0	1	2	3	negative
safe	-3	-2	-1	0	1	2	3	dangerous
attractive	-3	-2	-1	0	1	2	3	unattractive
mild	-3	-2	-1	0	1	2	3	harsh
agreeable	-3	-2	-1	0	1	2	3	disagreeable
active	-3	-2	-1	0	1	2	3	passive
easy	-3	-2	-1	0	1	2	3	hard
fast	-3	-2	-1	0	1	2	3	slow

Appendix 2.1

Socio-demographic Questionnaire.

Unit number ..... Post Code .....

We are conducting a survey in the gynaecology department to find out if we need to change the service that we provide for you. We are particularly interested in women who are coming to see us for the first time with heavy periods. We would be very grateful if you could complete this anonymous questionnaire which will help greatly our efforts to improve the service we provide.

(Tick one box for each question)

1. What age group are you in?
   - 20 - 29 ☐
   - 30 - 39 ☐
   - 40 - 49 ☐
   - 50 or over ☐

2. Do you have children?
   - none ☐
   - one ☐
   - two ☐
   - more than two ☐

3. How old were you when you completed your education?
   - 16 or less ☐
   - 17 to 18 ☐
   - 19 or over ☐

4. Are you working?
   - student ☐
   - unemployed ☐
   - part-time ☐
   - full-time ☐
   - housewife ☐

5. Which group fits you best?
   - single ☐
   - married / cohabiting ☐
   - widowed / separated ☐

6. What kind of house do you live in?
   - rented ☐
   - council ☐
   - own flat ☐
   - own house ☐
   - other (describe below) ☐

7. Do you smoke?
   - no ☐
   - less than ten a day ☐
   - more than ten a day ☐

8. How long have you had heavy periods?
   - Less than six months ☐
   - 6 - 12 months ☐
   - more than a year ☐

9. Have you seen a doctor, prior to this episode, regarding your heavy period?

yes ☐
no ☐

10. If yes, did the doctor prescribe tablets for them?

yes ☐
no ☐

11. Did you take the tablets as prescribed?

always ☐
sometimes forgot ☐
often forgot ☐
stopped them ☐

12 How many days each month do your periods stop you from performing normal daily activities?

none ☐
one day ☐
two days ☐
more than two days ☐

13. Following treatment for your heavy periods, what improvement in your symptoms do you expect?

bleeding: lighter periods / no bleeding at all

pain: less painful periods / no pain at all

answer question 14 only if you are not taking part in the trial comparing medical treatment with the transcervical resection of the endometrium (TCRE).

14. Did you feel unable to participate in the study comparing medical treatment to TCRE because -

you do not agree with medical trials? ☐
it would take up too much time? ☐
you specifically wanted a certain treatment? ☐
you did not want any treatment? ☐
you wanted the doctor to choose your treatment? ☐
other - (describe below) ☐

Appendix 2.2

Reasons for Preference

You have told us that you have a strong preference for a particular from of management for your heavy periods.
What things were important in making you decide this?

1. **The treatment was recommended by my family doctor** yes ☐ no ☐

2. **The treatment was recommended by a friend** yes ☐ no ☐

3. **I read about it in a magazine / saw it on TV** yes ☐ no ☐

4. **I did not want to take tablets at all** yes ☐ no ☐

5. **I did not want an operation at all** yes ☐ no ☐

6. **I have tried tablets and they did not work** yes ☐ no ☐

7. **Other reasons - please write below**

Appendix 3.1

TRANSCERVICAL RESECTION OF THE ENDOMETRIUM (T.C.R.E.)

WHAT IT IS :

T.C.R.E. is an operation which has become available for treating heavy periods. Instead of removing the whole womb, only the lining of the womb (endometrium) is removed. Rather than stopping the periods completely, although this does happen in some women, this operation makes your periods much lighter. Unless you have been sterilised already , there is still a chance of becoming pregnant after the operation, so you must continue using contraception. However , a sterilisation operation can be carried out at the same time as the T.C.R.E. if desired.

HOW IS IT DONE :

T.C.R.E. is usually done under a general anaesthetic and takes about 20 - 30 minutes. No cuts are required. When you are asleep, a telescope is passed through the neck of the womb (cervix) which allows the surgeon to see inside the womb. The womb is filled with fluid to help see clearly. The operation can then be performed by removing the endometrium from the whole of the inner surface of the womb. This is done using diathermy (an electric current) with a small metal loop passed down the telescope. The operation is easier if the endometrium is thin. Five weeks before the operation you will receive a drug which will make the endometrium thin.

It is important for you to be aware that, like any other operation, unexpected problems sometimes occur. During the operation, there is a slight possibility that some damage might be done to the wall of the womb. This usually means that the operation cannot be completed, but there is a very small risk that a bigger operation (such as a hysterectomy) might need to be carried out. This is only done if absolutely necessary.

WHAT TO EXPECT IMMEDIATELY AFTERWARDS :

When you wake up you may feel some cramp, like a period pain, and have some bleeding. Rarely , you may wake up with a catheter in the bladder or the womb. This is put in if you have absorbed fluid from the operation or if there has been bleeding, but is removed after a short time. Most women go home the same, or the next day.

WHAT HAPPENS AFTER GOING HOME ?

You may have some cramps for a few days. While the inside of the womb is healing , you will have a discharge from the vagina. This may last a few weeks and be quite watery, but this is normal. If it becomes nasty smelling and you get pain with it, then you should see your own doctor in case there is some infection. This is easily cleared up by a course of antibiotics. About one month after the operation it is usual to have a bleed like a period; this does not mean the operation hasn't worked.

WHEN CAN I GO BACK TO WORK ?
You can return to all normal everyday activities as soon as you feel able. The average time to get over this operation is 2 weeks.

WHEN WILL I KNOW IF THE OPERATION HAS BEEN A SUCCESS ?
Some people have no bleeding at all after this operation . More commonly the periods get gradually lighter over a few months, so if the first two periods don't seem much better, then it is worth waiting to see what happens over the next few months. In a few women, however, the lining of the womb grows back and the periods continue to be heavy. If this happens repeating the procedure can be successful, although we would discuss options with you.

WHAT ABOUT THE FUTURE ?
You will still need to have cervical smears as the neck of the womb is still present. When you reach the menopause, this operation does not prevent you from taking hormone replacement therapy, but discuss with your doctor which would be the best to take.

If you have any further questions, please ask to speak to one of the doctors.

Appendix 3.2

PATIENT INFORMATION SHEET

TRIAL OF MEDICAL TREATMENT VERSUS T.C.R.E. FOR HEAVY PERIODS

Your doctor has referred you to see a gynaecologist because of your heavy periods. Now that you have seen the specialist, you will have discussed the treatment options available to you (medical or surgical). There are a number of medical treatments available that can help your problem (these involve taking tablets). You may have to continue taking the tablets to keep the periods light. Surgical treatment includes hysterectomy, which is not felt necessary for you at present, or transcervical resection of the endometrium (T.C.R.E.). The other information sheet you were given explains how T.C.R.E. works and how it is performed. This operation can reduce your heavy monthly bleeding.

Both medical treatment and T.C.R.E. are recognised treatments for women with heavy periods, but at the moment it is not possible to say which one is better. To find out what is the best treatment, doctors need to perform a study. The most effective way to carry out this study is to ask women to have their treatment chosen by chance. This means that you would have a 50:50 (equal) chance of receiving either tablets or T.C.R.E..

If you are to receive medical treatment then the gynaecologist who saw you will prescribe a course of tablets for you. An explanation of how the tablets work, how they are taken and possible side effects will be given. The treatment should be continued for four months if possible. If you are to have a T.C.R.E., then arrangements will be made for you to have your operation in 6 - 8 weeks. Four months after your treatment you will be seen again to find out how effective and acceptable it has been. You can withdraw from the study at any time if you wish.

Appendix 3.3

TCRE / medical: recruitment questionnaire.

Study number		**Date of birth**	
Height (cms)		**Weight (kg)**	

1. Marital status

single		1
married		2
steady partner		3
separated		4
divorced		5
widowed		6

2. How long have you had heavy periods for?

Less than six months		1
six to twelve months		2
one to two years		3
two to five years		4
over five years		5

3. Are your periods regular? (once a month)

yes		1
no		2

4. How long is it from the first day of one period to the first day of the next?

more than six weeks		1
four to six weeks		2
three to four weeks		3
less than three weeks		4
totally unpredictable		5

5. How long do your periods last?

less than three days		1
three to five days		2
five to seven days		3
seven to ten days		4
more than ten days		5
no bleeding at all		6

6. For how many days is the period heavy? | | |

7. Are your periods painful?

yes		1
no		2
sometimes		3

8. If painful, for how many days do you have pain? | | |

9. Do you take pain-killers for period pain?

yes		1
no		2

10. For each day of your period please show how severe the symptoms were by giving a score of between 1 - 5 (1 = mild bleeding or pain, 5 = the worst bleeding or pain you can think of)

Day of period	bleeding score	pain score
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

11. Do you work?

yes ☐ 1
no ☐ 2

12. Do you take time of work with each period?

(if no go to question 15)

yes ☐ 1
no ☐ 2
sometimes ☐ 3

13. How many days off do you take on average?

☐☐

14. Is this because of pain, bleeding, or both?

pain ☐ 1
bleeding ☐ 2
both ☐ 3

15. Do you get any of the following symptoms before or during a period?

	Yes 1	No 2	
breast discomfort	☐	☐	1
bloatedness	☐	☐	2
irritability	☐	☐	3
headaches	☐	☐	4
depression	☐	☐	5

16. Do you get hot flushes or sweats?

yes ☐ 1
no ☐ 2
sometimes ☐ 3

17. **Do you have pain at intercourse?**

never	☐	1
sometimes	☐	2
often	☐	3
always	☐	4

18. **Have you had any drug treatment from your doctor for your heavy periods?**

yes	☐	1
no	☐	2

19. **If treated, which of the following tablets have you used, and what did they do for you?**

	yes	no	no benefit 1	slight benefit 2	great benefit 3	cured 4	side effects 5
non-steroidal (e.g. Ponstan, Brufen)	☐	☐	☐	☐	☐	☐	☐
progestogens (Provera, Primolut)	☐	☐	☐	☐	☐	☐	☐
danazol (Danol)	☐	☐	☐	☐	☐	☐	☐
tranexamic acid (Cyclokapron)	☐	☐	☐	☐	☐	☐	☐
ethamsylate (Dicynene0	☐	☐	☐	☐	☐	☐	☐
combined pill (contraceptive pill)	☐	☐	☐	☐	☐	☐	☐
other - please specify below	☐	☐	☐	☐	☐	☐	☐

.....

20. **What contraception do you use?**

none	☐	1
condoms	☐	2
diaphragm	☐	3
combined pill	☐	4
mini pill	☐	5
coil	☐	6
sterilised	☐	7
partner had vasectomy	☐	8
depot provera	☐	9

21. **How many children have you had?** ☐☐

22. **Have you had any gynaecological operations?**

no	☐
d & c	☐
sterilisation	☐
caesarean section	☐
laparoscopy	☐
cone biopsy	☐
other - describe below	☐

Appendix 3.4 TCRE / medical: four month follow-up questionnaire.

1. Following your treatment have your periods

stopped?	1
continued, but lighter?	2
stayed the same?	3
continued, but heavier	4

if your periods have stopped go to question 8

2. How long is it from the first day of one period to the first day of the next?

more than six weeks	1
four to six weeks	2
three to four weeks	3
less than three weeks	4
totally unpredictable	5

3. How long do your periods last?

less than three days	1
three to five days	2
five to seven days	3
seven to ten days	4
more than ten days	5

4. For how many days is the period heavy? ☐☐

5. Do you have pain with your period?

no	1
less than before	2
same as before	3
worse than before	4

6. If painful, for how many days do you have pain? ☐☐

7. Do you take pain-killers for period pain?

yes	1
no	2

8. For each day of your period please show how severe the symptoms were by giving a score of between 1 - 5 (1 = mild bleeding or pain, 5 = the worst bleeding or pain you can think of)

Day of period	bleeding score	pain score
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

7. Do you take time of work with each period?

yes	☐	1
no	☐	2
sometimes	☐	3

8. Do you get any of the following symptoms before or during a period?

	Yes 1	No 2	
breast discomfort	☐	☐	1
bloatedness	☐	☐	2
irritability	☐	☐	3
headaches	☐	☐	4
depression	☐	☐	5

9. Do you get hot flushes or sweats?

yes	☐	1
no	☐	2
sometimes	☐	3

10. Do you have pain at intercourse?

never	☐	1
sometimes	☐	2
often	☐	3
always	☐	4
does not apply	☐	5

11. Since treatment are you experiencing any new or different pelvic pain?

no	☐	1
sometimes	☐	2
continually	☐	3

12. Overall, what effect has the treatment had on your symptoms?

worse	☐	1
no effect	☐	2
improved, but not sufficiently	☐	3
improved to an acceptable level	☐	4
cured completely	☐	5

13. Did you find the treatment acceptable?

yes	☐	1
no	☐	2

14. If not acceptable, then why was this?
tick all that apply

treatment unpleasant	☐	1
did not help the bleeding	☐	2
did not help the pain	☐	3
side effects were bad	☐	4
did not want any periods	☐	5
other - please describe below	☐	6

15. If you ticked side effects for question 14, please write what they were below

16. If your treatment involved taking tablets, did you

always take them as prescribed	☐	1
occasionally missed them	☐	2
regularly missed them	☐	3
stopped them	☐	4

17. Would you be prepared to continue with the same treatment or have it again if necessary

yes	☐	1
no	☐	2

18. Please indicate how you would rate your overall satisfaction with your treatment.
(please circle the number that is closest for you)

1	2	3	4	5	6
totally satisfied	generally satisfied	fairly satisfied	fairly dissatisfied	generally dissatisfied	totally dissatisfied

19. Please indicate the severity of your symptoms now
(please circle the number that is closest for you)

1	2	3	4	5
none	mild	moderate	severe	very severe

Appendix 4. TCRE / medical: two year follow-up questionnaire.

Your original treatment in this trial was.....

1. Have your periods

stopped?	☐	1
continued, but lighter?	☐	2
stayed the same?	☐	3
continued, but heavier	☐	4

if your periods have stopped go to question 8

2. How long is it from the first day of one period to the first day of the next?

more than six weeks	☐	1
four to six weeks	☐	2
three to four weeks	☐	3
less than three weeks	☐	4
totally unpredictable	☐	5

3. How long do your periods last?

less than three days	☐	1
three to five days	☐	2
five to seven days	☐	3
seven to ten days	☐	4
more than ten days	☐	5

4. For how many days is the period heavy? ☐☐

5. Do you have pain with your period?

no	☐	1
less than before	☐	2
same as before	☐	3
worse than before	☐	4

6. For each day of your period please show how severe the symptoms were by giving a score of between 1 - 5 (1 = mild bleeding or pain, 5 = the worst bleeding or pain you can think of)

Day of period	bleeding score	pain score
1	☐	☐
2	☐	☐
3	☐	☐
4	☐	☐
5	☐	☐
6	☐	☐
7	☐	☐
8	☐	☐
9	☐	☐
10	☐	☐

7. Do your periods stop you from carrying out your work, housework or daily activities?

no, not at all	☐	1
no, but work suffers	☐	2
yes, but only one day	☐	3
yes, more than one day	☐	4

8. What further treatment have you had for your periods since the original treatment you were given in the study (see start if you can't remember)

none	☐	1
different tablets	☐	2
TCRE operation	☐	3
repeat TCRE	☐	4
hysterectomy	☐	5

9. Do you get any of the following symptoms before or during a period?

	Yes 1	**No 2**	
breast discomfort	☐	☐	1
bloatedness	☐	☐	2
irritability	☐	☐	3
headaches	☐	☐	4
depression	☐	☐	5

10. Do you have pain at intercourse?

no	☐	1
yes, but less than before	☐	2
yes, the same as before	☐	3
yes, worse than before	☐	4

11. Since treatment are you experiencing any new or different pelvic pain?

no	☐	1
sometimes	☐	2
regularly	☐	3

12. Overall, what effect has the treatment had on your symptoms?

worse	☐	1
no effect	☐	2
improved, but not sufficiently	☐	3
improved to an acceptable level	☐	4
cured completely	☐	5

13. Did you find the treatment acceptable?

yes	☐	1
no	☐	2

14. What treatment would you recommend to a friend with heavy periods?

medical (tablets)	☐	1
TCRE operation	☐	2
hysterectomy	☐	3
none	☐	4

15. Please indicate how you would rate your overall satisfaction with your treatment.
(please circle the number that is closest for you)

1	2	3	4	5	6
totally satisfied	generally satisfied	fairly satisfied	fairly dissatisfied	generally dissatisfied	totally dissatisfied

Appendix 5.1 PATIENT INFORMATION SHEET

study of transcervical resection of the endometrium (T.C.R.E). versus microwave endometrial ablation (M.E.A.)

Each month a lining (endometrium) forms inside the womb and is shed as your period. Sometimes this bleeding can become heavy and even unpredictable. Removing this lining can result in periods stopping altogether or becoming lighter. It has been decided that this is the most appropriate treatment for your heavy periods.

There are many different ways of removing the endometrium. They are all performed by passing an instrument up through the neck of the womb (cervix) whilst you are asleep. The commonest method at present is to perform a T.C.R.E. which involves removing the lining using a small electric loop. This has been proven to be a successful and acceptable treatment. A newer method of removing the lining has been developed which involves using a small microwave probe (M.E.A.). The energy waves produced cause the endometrium to be destroyed to a similar depth as T.C.R.E.. This new microwave technique seems to be just as effective and safe at treating heavy periods as T.C.R.E., but it may be quicker and easier to use.

To find out how useful M.E.A. is doctors need to do a study. If you were to take part in the study you would be allocated to having one or other operations by chance. This means that you would have a 50:50 chance of having a T.C.R.E. or a M.E.A.. We would ask you to complete questionnaires before the operation and at six and twenty-four months afterwards. These would allow us to find out how effective M.E.A. is at treating heavy periods and also how acceptable it is. You would be able to withdraw from the study at any time if you wished.

It is important to add that neither operation guarantees that you can not fall pregnant in the future, although it is unlikely. If you wish, a sterilisation can be performed at the same time as the operation which should not increase your stay in hospital.

Appendix 5.2 M.E.A. versus T.C.R.E. trial: recruitment questionnaire

Unit number ..... **Study number** .....

Date of birth ..... **Date of clinic** .....

Parity ..... **Weight (kg)** .....

1/ How long have you had trouble with your periods?

- less than 1 year ☐ 1
- 1 to 3 years ☐ 2
- more than 3 years ☐ 3

2/ On average, are your periods regular or irregular ?

- regular ☐ 1
- irregular ☐ 2

3/ How many days are there from the first day of one period to the first day of the next ?

- less than 21 ☐ 1
- 21 to 35 ☐ 2
- more than 35 ☐ 3

4/ Would you describe your periods as

- light ☐ 1
- moderate ☐ 2
- heavy ☐ 3
- very heavy ☐ 4

5/ On average, for how many days does your period last ?

- less than 3 days ☐ 1
- between 3 and 7 days ☐ 2
- between 8 and 10 days ☐ 3
- more than 10 days ☐ 4

6/ On average, for how many days is the bleeding heavy ?

- not heavy ☐ 1
- 1 to 3 days ☐ 2
- 4 to 6 days ☐ 3
- 7 or more days ☐ 4

7/ Imagine an average period for you ; for each day please show how severe your bleeding and pain were by giving each day a score from 1 to 5 (1 is mild bleeding/pain, increasing up to 5, the worst bleeding/pain you can think of)

Day of Period	Bleeding score	Pain score
1	☐	☐
2	☐	☐
3	☐	☐
4	☐	☐
5	☐	☐
6	☐	☐
7	☐	☐
8	☐	☐
9	☐	☐
10	☐	☐

8/ Are your periods usually painful ?

- yes ☐ 1
- no ☐ 2

9/ Do your periods stop you from carrying out your work, housework or other daily activities ?

- no, not at all ☐ 1
- no, but work suffers ☐ 2
- yes, but only one day ☐ 3
- yes, more than one day ☐ 4

10/ Do your periods interfere with leisure activities ?

- no, not at all ☐ 1
- mildly affected ☐ 2
- moderately affected ☐ 3
- severely affected ☐ 4
- totally prevents it ☐ 5

11/ Do your periods affect your sex life ?

- no, not at all ☐ 1
- mildly affected ☐ 2
- moderately affected ☐ 3
- severely affected ☐ 4
- totally prevents it ☐ 5

12/ At any time in the last three months, have you needed to use more than one form of protection at the same time

- no ☐ 1
- tampon and pads ☐ 2
- two pads ☐ 3
- tampon and two pads ☐ 4
- more than this (e.g. towel) ☐ 5

13/ Do you get any of the following symptoms just before or during a period ?

	Yes	No
breast discomfort	☐	☐
bloatedness	☐	☐
irritable	☐	☐
headaches	☐	☐
depression	☐	☐

14/ Do you have any of these bladder problems ?

	Yes	No
a/ leaking when coughing or straining	☐	☐
b/ leaking before you make it to the toilet	☐	☐
c/ going frequently (more than 7 times/day)	☐	☐
d/ getting up more than once a night	☐	☐

15/ Do you have problems with your bowels ?

- none ☐ 1
- constipation ☐ 2
- diarrhoea ☐ 3

16/ Is sexual intercourse usually painful for you ?

- Yes ☐ 1
- No ☐ 2

Appendix 5.3

M.E.A. versus T.C.R.E. study
Operative Questionnaire

Please complete the relevant portions of this questionnaire at the time of the operation and then put it in the case notes. The clinical research fellow will complete the rest of it and make follow up arrangements.

Operative Details for coding **yes = 1** **no = 2**

Day Case Yes / No Study number .....

Antibiotics Yes / No Unit number .....

Randomised M.E.A.(**1**) / T.C.R.E.(**2**) Date of operation .....

1/ Operating time taken .....mins

2/ Total time (operating and anaesthetic) .....mins

3/ Intraoperative complications ? Yes / No
if yes, tick appropriate boxes

failed instrumentation	☐	1
uterine perforation	☐	2
inadequate view	☐	3
haemorrhage	☐	4
equipment failure	☐	5
bowel damage	☐	6
urinary tract damage	☐	7
fluid overload	☐	8
major vessel damage	☐	9
uterine catheter required	☐	10
other (specify below)	☐	11

.....

4/ If uterine perforation occurred was it

with sound	☐	1
with dilator	☐	2
with hysteroscope	☐	3
with M.E.A. probe	☐	4
with resectoscope	☐	5

5/ Procedure abandoned ? Yes / No

6/ For T.C.R.E., fluid deficit post procedure .....mls

7/ Laparoscopy performed ? Yes / No

8/ If yes, was this

planned diagnostic	☐ 1
emergency diagnostic	☐ 2
sterilisation	☐ 3
L.U.N.A.	☐ 4

9/ Actual treatment received ?

M.E.A.	☐ 1
T.C.R.E.	☐ 2
Hysterectomy	☐ 3

10/ Findings at hysteroscopy ?

Normal cavity	☐ 1
Irregular cavity	☐ 2
Submucous fibroid	☐ 3
Uterine septum	☐ 4

11/ If fibroids how many > 2cms ? .....

12/ Cavity length .....cms

13/ Postoperative complications ? Yes / No
if yes, what ?

Chest infection	☐ 1
U.T.I.	☐ 2
Return to theatre	☐ 3
D.V.T.	☐ 4
P.E.	☐ 5
Pulmonary oedema	☐ 6
Uterine bleeding	☐ 7
Uterine infection	☐ 8
Admitted to I.T.U.	☐ 9
Other, explain below	☐ 10

.....

14/ Was post operative pain relief required on the ward? Yes / No

if yes, what was the strongest required ?

Oral	☐ 1
Suppository, e.g. Voltarol	☐ 2
Injectable	☐ 3

15/ Post operative hospital stay .....days .....nights total.....hours

16/ Was readmission required ? Yes / No
if yes, why ?

.....

Appendix 5.4 M.E.A. versus T.C.R.E. study: 4 month follow-up questionnaire

Unit number ..... **Study number** .....

Date of clinic .....

It is now four months since your operation for heavy periods. We would be grateful if you would complete the following questionnaire for us.

1/ How long after the operation did you feel that you had completely recovered ?

I have not recovered yet	☐	1
less than 2 weeks	☐	2
2 to 4 weeks	☐	3
4 to 8 weeks	☐	4
2 to 3 months	☐	5
3 to 4 months	☐	6

2/ When were you able to return to your normal everyday activities (housework, work etc.)

less than 2 weeks	☐	1
2 to 4 weeks	☐	2
4 to 8 weeks	☐	3
2 to 3 months	☐	4
3 to 4 months	☐	5
still unable	☐	6

3/ Have your periods

stopped	☐	1
continued but lighter	☐	2
continued as before	☐	3
continued but heavier	☐	4

*** if stopped, then go straight to question 13***

4/ How many days are there from the first day of one period to the first day of the next ?

less than 21	☐	1
21 to 35	☐	2
more than 35	☐	3

5/ On average, for how many days does your period last ?

less than 3 days	☐	1
between 3 and 7 days	☐	2
between 8 and 10 days	☐	3
more than 10 days	☐	4

6/ On average, for how many days is the bleeding heavy ?

not heavy	☐	1
1 to 3 days	☐	2
4 to 6 days	☐	3
7 or more days	☐	4

7/ Do you have pain with your period ?

no	☐
less than before	☐
same as before	☐
worse than before	☐

8/What is an average period like for you now ? For each day please show how severe your bleeding and pain are by giving each day a score from 1 to 5 (1 is mild bleeding/pain, increasing up to 5, the worst bleeding/pain you can think of)

Day of Period	Bleeding score	Pain score
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

9/ Do your periods stop you from carrying out your work, housework or other daily activities ?

- no, not at all ☐ 1
- no, but work suffers ☐ 2
- yes, but only one day ☐ 3
- yes, more than one day ☐ 4

10/ Do your periods interfere with leisure activities ?

- no, not at all ☐ 1
- mildly affected ☐ 2
- moderately affected ☐ 3
- severely affected ☐ 4
- totally prevents it ☐ 5

11/ Do your periods affect your sex life ?

- no, not at all ☐ 1
- mildly affected ☐ 2
- moderately affected ☐ 3
- severely affected ☐ 4
- totally prevents it ☐ 5

12/ At any time in the last three months, have you needed to use more than one form of protection at the same time

- no ☐ 1
- tampon and pads ☐ 2
- two pads ☐ 3
- tampon and two pads ☐ 4
- more than this (e.g. towel) ☐ 5

13/ Do you get any of the following symptoms just before or during a period ?

	Yes	No
breast discomfort		
bloatedness		
irritability		
headaches		
depression		

14/ Do you have any of these bladder problems ?

	Yes	No
a/ leaking when coughing or straining	☐	☐
b/ leaking before you make it to the toilet	☐	☐
c/ going frequently (more than 7 times/day)	☐	☐
d/ getting up more than once a night	☐	☐
e/ having to run to the toilet quickly	☐	☐

15/ Do you have problems with your bowels ?

none	☐ 1
constipation	☐ 2
diarrhoea	☐ 3

16/ Is sexual intercourse painful for you ?

no	☐ 1
yes, but less than before	☐ 2
yes, the same as before	☐ 3
yes, worse than before	☐ 4

17/Since the operation are you experiencing any new or different pelvic pain ?

no	☐ 1
sometimes	☐ 2
regularly	☐ 3
continually	☐ 4

18/ Overall, what effect has the operation had on your symptoms ?

No effect	☐ 1
improved, but not sufficiently	☐ 2
improved to an acceptable level	☐ 3
cured completely	☐ 4

19/ Did you find the operation acceptable ?

Yes	☐ 1
No	☐ 2

20/ Would you recommend this treatment to a friend with heavy periods

Yes	☐ 1
No	☐ 2

21/ Please indicate how you would rate your overall satisfaction with your treatment.
(please circle the number that is closest for you)

1	2	3	4	5	6
totally satisfied	generally satisfied	fairly satisfied	fairly dissatisfied	generally dissatisfied	totally dissatisfied

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The impact of using a partially randomised patient preference design when evaluating alternative managements for heavy menstrual bleeding

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Objective To identify the advantages and disadvantages of using a partially randomised patient preference design rather than a conventional randomised controlled design when evaluating alternative managements for heavy menstrual bleeding.

Design Randomised controlled comparison of two clinical trial designs with subsequent follow up of the cohorts of women generated.

Participants Women attending a general gynaecology clinic for the first time because of heavy menstrual bleeding.

Interventions Partially randomised patient preference clinical trial design and conventional randomised controlled design.

Main outcome measures Overall participation; participation in randomised clinical trial of medical management compared with transcervical surgical resection of the endometrium; prognostic characteristics (socio-demographic and Short Form 36) of clinical trial groups; outcomes (clinical and Short Form 36) of clinical trial groups.

Results Overall, more women participated in the partially randomised patient preference design (130/135 *vs* 97/138; difference 27%, 95% CI 18% to 34%) but there was no difference in the numbers who agreed to be randomised (90/135 *vs* 97/138; difference −3%, 95% CI −15% to 7%). Women who chose medical management tended to have better general health, to be less restricted by their menstrual problems, with fewer having been previously treated by their general practitioner. Those who chose transcervical resection of the endometrium had all tried medical management and had higher bleeding scores. Follow up satisfactions and acceptability rates, and Short Form 36 scores were highest after transcervical resection of the endometrium, whether chosen or randomised. Acceptability and a desire to continue the same treatment was greater among those who chose medical management than those randomly allocated it.

Conclusions Use of the partially randomised patient preference design did not affect recruitment to the randomised controlled trial suggesting that a conventionally designed trial would not be biased by motivational factors in this context. Data from the preference groups informed the generalisability of the results but did tend to confirm conclusions that anyway reasonably followed from the randomised controlled trial. The extra resource implications of using the partially randomised patient preference design were significant reflecting the additional 40% who participated and the extra analyses entailed.

INTRODUCTION

It is widely accepted that a randomised controlled trial is usually the research design of choice when evaluating a new treatment or comparing management policies. A potential problem with this design is that to be recruited a participant must be prepared to accept any of the health care options being compared. Eligible women may, however, have strong opinions regarding the relative acceptability of treatments[1,2]. This may lead to the recruits being a small proportion of those otherwise eligible, which could affect the generalisability of results. Also, some people who agree to randomisation may do so in an effort to obtain the new or alternative therapy. This may be especially true when participating in the trial is the only way of getting the new treatment, or allows it to be obtained earlier. In this case, randomisation will initially create like groups until the allocated treatment is known when those allocated their preferred treatment may be pleased while those who receive the alternative management may be disappointed[3]. Despite

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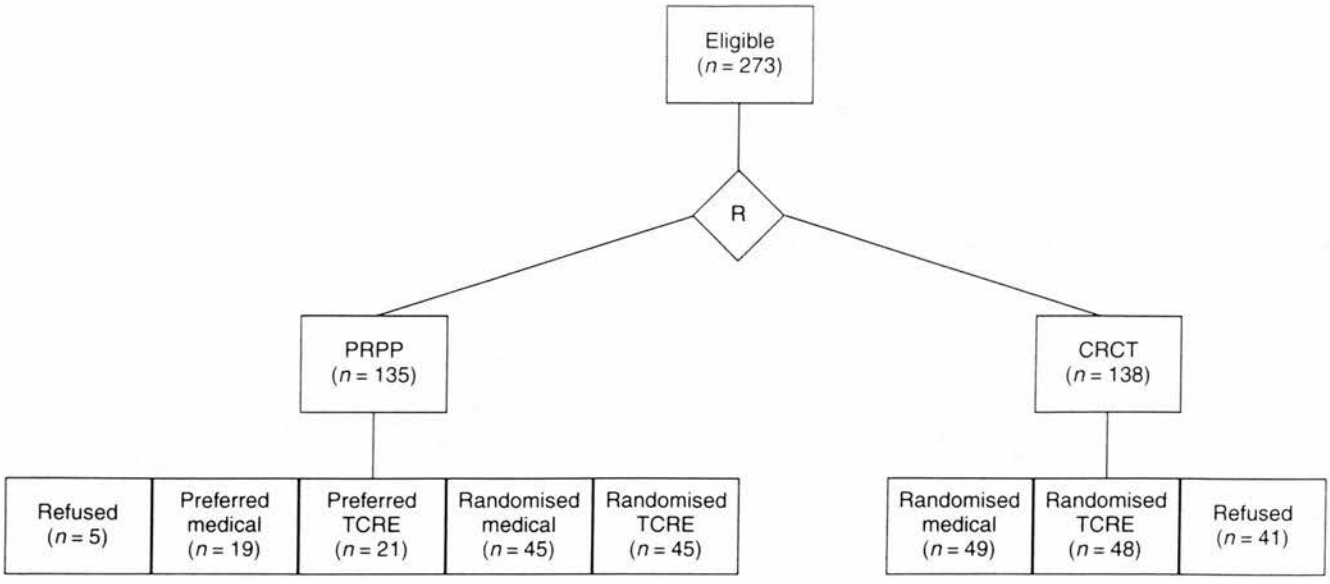

Fig. 1. Derivation of study cohorts. TCRE = transcervical resection of the endometrium; PRPP = partially randomised patient preference; CRCT = conventional randomised controlled trial.

random allocation, the trial groups may then differ in respect of motivation. If those disappointed with the allocation tended to decide to withdraw, this would introduce selection bias. Additionally, motivational differences could affect compliance with the allocated management, particularly when the treatments under investigation differ dramatically[4,5] and when evaluating participative interventions[6]. Motivation may also introduce bias in the measurement of outcome particularly if these measures are subjectively assessed by those participating in the trial; this applies, for example, to treatment success, satisfaction, acceptability and quality of life following management of menstrual disorders[7].

The partially randomised patient preference (PRPP) trial design[6] aims to deal with these issues. Potential participants with a strong preference for one or other treatment receive it, while the remainder, without a preference, are randomised. Two groups of recruits are generated in whom motivational factors are optimised by allowing them to have their preferred treatment, while two randomised groups are created in whom motivational factors are equalised (Fig. 1). There are a number of putative advantages: larger numbers of people are likely to participate in the overall study; analysis of the randomised groups will allow relatively unbiased measurement of any differential effects of the treatments; the preference groups, which can be viewed as part of a nonrandomised prospective cohort study, may give information on the factors which determine preference or refusal to be randomised; and the effects of motivational factors on outcome can be addressed by comparing those who chose a treatment with those who were randomly allocated to that treatment[8].

Nevertheless, the value of the PRPP design remains controversial. Not only do the preference arm comparisons have all the potential limitations of observational studies[9] (which randomisation aims to avoid), but making preference choices could reduce the number of people recruited to the randomised comparison[5,10,11]. This in turn would reduce the statistical power and might if motivation is not a strong influence on outcome, reduce rather than increase the generalisability. The resources required are also greater; arguably, these may be better used to increase the size of the randomised comparison to give clearer, more precise information.

We explored these issues in the context of a comparison of medical management with hysteroscopic treatment of heavy menstrual bleeding, a condition where the issues of patient preference are felt to be important[12]. The results of the randomised comparison are reported in detail in the accompanying report. In the element of the study reported here, we assessed the impact of using a PRPP design by addressing the following questions:

1. Do more people participate in a PRPP study than in a conventional randomised controlled trial?
2. Does making the option of preferred management more explicit reduce the number of people who agree to be randomised? If so, does this change the characteristics of the group who make up the randomised comparison?
3. Are there differences between the preference and randomised groups at trial entry? If so, does knowing about them improve the interpretation and usefulness of the study?
4. Are there differences between the preference groups and randomised groups in outcome? If so, does knowing about them improve the interpretation and usefulness of the study?

5. If the interpretation and usefulness of the study is improved by the PRPP design, is this worth the extra resources required for a PRPP design?

METHODS

From 1 October 1994 to 30 September 1995, women with heavy menstrual loss who were first time attenders at the clinic of nine of eleven general gynaecologists in a single University hospital were identified by screening referral letters. Following local research ethics committee approval, the women were randomly allocated to either a PRPP or a conventional randomised controlled trial design. Formal entry and randomisation was signalled by opening the next in a series of sealed, opaque envelopes. The allocation sequence was pre-determined from a computer generated list of numbers. A woman's hospital notes were then labelled to identify the type of trial design to which she had been allocated. Importantly, at this stage, the women were unaware that they were participating in a randomised trial.

Once a gynaecologist had checked that a potential participant had none of the exclusion criteria (a uterus larger than ten weeks of gestational size, fertility desired, specifically referred for surgical treatment, requesting hysterectomy, or a finding of significant gynaecological pathology), she was informed of the different treatments available within the clinical trial (medical management or transcervical resection of the endometrium (TCRE)) and given the patient information sheet corresponding to her allocated study design. These information sheets outlined the reasons for undertaking the trial, the timescale, the treatments available within the trial, and the principle of randomisation. The patient information sheet for the PRPP trial differed from that of the conventional randomised controlled trial by only two sentences which read: 'We do realise that some women may have a preference for one of the treatments. If you feel strongly that you want one treatment in particular, then please tell us'. All the women were then seen by the same investigator. Those in the conventional randomised controlled trial arm were told about randomisation and its importance to the trial. Those in the PRPP arm were counselled in a similar way, but it was also pointed out that if they had a strong preference for one of the treatments then they could have it. All women, whether or not recruited, completed a questionnaire which described certain socio-demographic and clinical characteristics. It also specifically asked those who did not agree to join the study why they had decided this. Informed consent was obtained from those agreeing to participate in the clinical trial. Participants had their haemoglobin level measured and completed a trial booklet which contained a detailed clinical questionnaire (including expectations of treatment), the hospital anxiety and depression scale[13], and Short Form 36 health survey[14–16]. These measurements except hospital anxiety and depression scale were repeated four months after starting treatment to assess outcome.

Table 1. Baseline characteristics of all eligible women by allocated trial design. Values are given as *n* (%). PRPP = partially randomised patient preference; CRCT = conventional randomised controlled trial.

	PRPP ($n = 135$)	CRCT ($n = 138$)
Age < 40	50 (37)	42 (30)
Two or more children	113 (84)	114 (83)
Married	117 (87)	122 (89)
Living in own property	88 (67)	98 (72)
Unemployed	24 (18)	31 (23)
Smoker	53 (42)	46 (35)
Heavy periods > 1 year	113 (84)	103 (75)
Previous medical treatment	107 (80)	103 (76)

Women who agreed to random allocation to medical management or TRCE were managed accordingly. Those in the PRPP group who expressed a preference received the treatment chosen. Those who refused to participate were referred back to their original gynaecologists for treatment (most of whom did not perform TCREs).

The sample size was largely dictated by the numbers of participants sought in the randomised clinical trial (see accompanying report). However, the sample size of 270 for the study reported here had over 95% power to detect a difference in participation rates of 20%; 85% power for a 15% difference; and 50% power for a 10% difference (all $2P < 0{\cdot}05$). Comparisons of categorical data were made using the χ^2 test, and of continuous data with normal distribution, using Student's t test. Changes over time were compared for categorical variables using McNemar's test and for continuous variables using Student's paired t test.

RESULTS

A total of 273 women were eligible for the study; 135 were randomised to the PRPP design and 138 to the conventional randomised controlled trial design. Figure 1 shows the allocation of women within the trial and Table 1 shows the baseline characteristics and comparability of these groups.

Of the 135 in the PRPP arm 90 (66·7%) agreed to be randomised and 40 (30%) expressed a definite preference, so the total number participating was 130 (96·7%) (Table 2). 97 (70%) of the 138 eligible in the conventional randomised controlled trial group agreed to participate all being randomised (difference in overall participation 27%, 95% CI 18% to 34%). There was,

Table 3. Characteristics of participating women by study group. Note: Randomised medical and randomised transcervical resection of the endometrium (TCRE) groups from both trial designs (PRPP and CRCT) have been combined as there are no significant differences between these groups for any descriptive variable. Values are given as *n* (%) or score [SD]. Key as for Table 1; HADS = hospital anxiety and depression scale; GP = general practitioner.

	Preferred medical ($n = 19$)	Preferred TCRE ($n = 21$)	Randomised medical ($n = 94$)	Randomised TCRE ($n = 93$)	Refused CRCT ($n = 41$)
Age < 40	7 (37)	8 (38)	31 (33)	29 (31)	15 (37)
Two or more children	14 (74)	15 (71)	82 (87)	81 (87)	31 (78)
Married	18 (95)	17 (81)	79 (84)	84 (90)	37 (93)
Living in own property	15 (83)	12 (60)	63 (68)	63 (69)	28 (68)
Unemployed	4 (21)	2 (10)	21 (22)	19 (21)	11 (25)
Smoker	8 (44)	6 (33)	34 (38)	39 (45)	12 (30)
Heavy periods > 1 year	17 (89)	19 (90)	71 (76)	79 (85)	26* (63)
> 1 GP consultation for menorrhagia	17 (89)	19 (90)	86 (91)	86 (92)	31* (76)
Previous medical treatment	11 (63)	19* (100)	73 (78)	77 (83)	28 (70)
Restricted for ≥ 2 days	8 (44)	13 (67)	60 (64)	62 (69)	24 (60)
Hoping for amenorrhoea	0 (0)	5* (24)	6 (6)	8 (9)	
Bleeding score	24 [8·26]	31 [9·13]	24 [8·52]	25 [7·59]	
Pain score	14 [10·2]	20 [14·3]	15 [9·53]	14 [10·7]	
HADS					
Anxiety	7·1*	8·9	8·2	8·9	
Depression	4·1	5·7	6·1	5·3	

*Significant results ($P < 0·05$).

Table 2. Numbers in the study groups and reasons for not participating. Values are given as *n* (%). Key as for Table 1; TCRE = transcervical resection of the endometrium.

	PRPP ($n = 135$)	CRCT ($n = 138$)	% difference {95% CI}
Study arm			
Preferred medical	19 (14)		
Preferred TCRE	21 (16)		
Randomised medical	45 (33)	49 (35)	
Randomised TCRE	45 (33)	48 (35)	
Refused	5 (3)	41 (30)	
Wanted tablets	0	17	
Wanted surgery	0	19	
Wanted doctor to choose	1	1	
Wanted no treatment	4	4	
TOTAL			
Recruited	130 (97)	97 (70)	−27 {−18 to −34}
Randomised	90 (67)	97 (70)	−3 {−15 to +7}

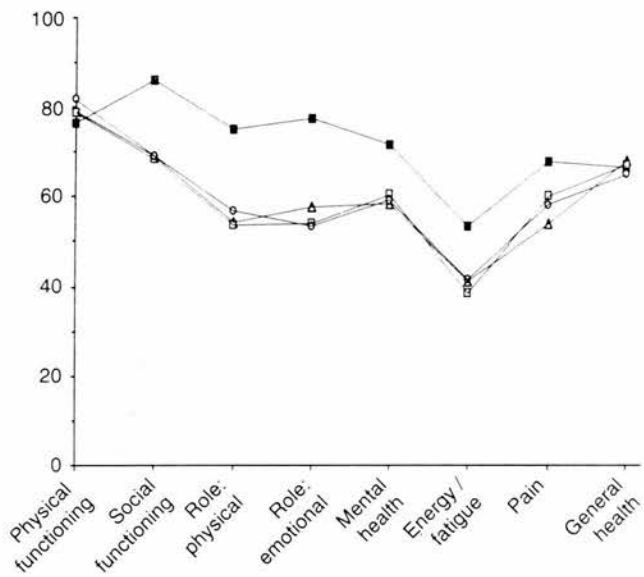

Fig. 2. Baseline Short Form 36 scores. ■ = prefers medical; □ = randomised medical; Δ = prefers TCRE; ○ = randomised TCRE.

however, no clear difference in the numbers of women who agreed to be randomised (difference −3%, 95% CI −15% to +7%). Of those within the conventional randomised controlled trial arm who refused to participate, 17 wanted medical treatment and 19 TCRE; this was similar to the numbers who chose their treatments in the PRPP cohort. Of those who agreed to participate, no woman in the PRPP group and one woman in the conventional randomised controlled trial group subsequently 'dropped out'.

Characteristics of the groups at the start of the study are shown in Table 3. The social, demographic and clinical characteristics and baseline Short Form 36 scores (Fig. 2) of those agreeing to randomisation within the PRPP design were very similar to those in the conventional randomised controlled trial group and data for these groups have therefore been combined in Table 3 to form randomised medical and randomised TCRE groups. Compared to those randomised, women who refused randomisation in the conventional randomised controlled trial group were significantly less likely to have had heavy periods for more than one year and to have consulted their general practitioner more than once

Table 4. Outcome four months after starting treatment. Values are given as *n* (%), reduction mean [SD] or increase ¦SD¦. TCRE = transcervical resection of the endometrium.

	Preferred medical (*n* = 19)	Randomised medical (*n* = 94)	Preferred TCRE (*n* = 21)	Randomised TCRE (*n* = 93)
Bleeding score	7·36† [9·44]	6·08‡ [11·26]	24·31‡ [11·41]	20·00‡ [8·76]
Pain score	2·78 [8·27]	5·31‡ [10·57]	14·63‡ [12·82]	10·53‡ [12·17]
Haemoglobin increase (g/dL)	−0·29 ¦0·99¦	0·18 ¦1·29¦	0·33 ¦1·07¦	0·76‡ ¦1·62¦
Satisfied with treatment	8 (42)	25 (27)	15 (71)	70 (76)
Treatment acceptable	12 (63)	33 (36)	17 (81)	86 (93)
Continue same treatment	12 (63)	29 (31)	16 (76)	86 (93)

Significant changes from baseline scores: *$P < 0·05$; †$P < 0·01$; ‡$P < 0·001$

Table 5. Mean change in Short Form 36 scores at 4 months. Values are given as score [SD]. Key as for Table 4.

	Preferred medical (*n* = 19)	Randomised medical (*n* = 94)	Preferred TCRE (*n* = 21)	Randomised TCRE (*n* = 93)
Physical functioning	6·58 [16·51]	4·84* [16·72]	12·86* [27·68]	10·16† [16·51]
Social functioning	8·19* [25·08]	7·57* [26·26]	19·05† [23·35]	17·44† [25·08]
Role physical	10·52 [38·23]	15·32* [46·78]	35·71† [45·12]	32·26† [38·23]
Role emotional	−1·75 [45·94]	8·96* [49·43]	30·16* [49·33]	31·54† [45·94]
Mental health	−0·84 [19·00]	4·78* [16·69]	10·1* [20·77]	15·01† [19·00]
Energy / fatigue	4·47 [20·76]	7·07* [20·23]	21·67† [20·70]	20·53† [20·76]
Pain	−0·58 [31·33]	8·84* [26·39]	12·7* [22·85]	21·62† [31·33]
General health	5·47* [20·85]	−0·25 [15·99]	6·71 [15·62]	10·49† [20·85]

Significant changes in scores: *$P < 0·05$; †$P < 0·01$.

regarding their heavy periods. They were also less likely to be smokers or to have received treatment for excessive menstruation previously ($P = 0·06$ and $P = 0·08$, respectively). Those in the preferred TCRE group had previously received treatment for heavy periods, were more likely to hope for amenorrhoea (despite choosing to avoid hysterectomy), and had higher baseline bleeding and pain scores than those randomised or preferring medical treatment. The preferred medical group scored significantly better than the other groups in all components of Short Form 36 except physical functioning and general health (Fig. 2) while their hospital anxiety and depression scale anxiety scores were also significantly better than those randomised or preferring TCRE (Table 3).

Outcome for the randomised groups has been described in detail in the accompanying paper; in summary there were highly significant differences in favour of TCRE for all parameters measured, including all eight components of Short Form 36 (Tables 4 and 5). There were no significant differences between those preferring TCRE and those randomised to this group, although satisfaction and acceptability levels were lower in the preferred TCRE group, reflecting a greater desire for amenorrhoea and subsequent requests for hysterectomy (5/21 women). Comparison of those who preferred medical treatment with those randomised to medical showed that women in the preference arm were significantly more likely to find the treatment acceptable and want to continue with it. They were also more likely to be satisfied with treatment, although this difference was not conventionally significant. Follow up Short Form 36 scores were also higher in the preferred medical arm (Fig. 3), but changes in Short Form 36 scores are difficult to compare as scores in the preference arm were significantly higher at baseline for six of the eight components. Nevertheless, women in the preferred medical group still had significantly poorer results for all parameters outlined on Table 4 than those randomised to TCRE (ranging from $P = 0·014$ for change in haemoglobin concentration to $P < 0·001$ for bleeding score, acceptability and continuation). Follow up Short Form 36 scores were higher for all parameters except social functioning in those randomised to TCRE (Fig. 3).

DISCUSSION

We decided in advance to assess the advantages and disadvantages of using a PRPP design in a comparison of alternative managements of heavy menstrual bleeding. We believe that this is the first randomised controlled comparison of the two designs.

Not surprisingly, we found that nearly all women in the PRPP group (97%) agreed to participate in the study compared with 70% in the conventional randomised

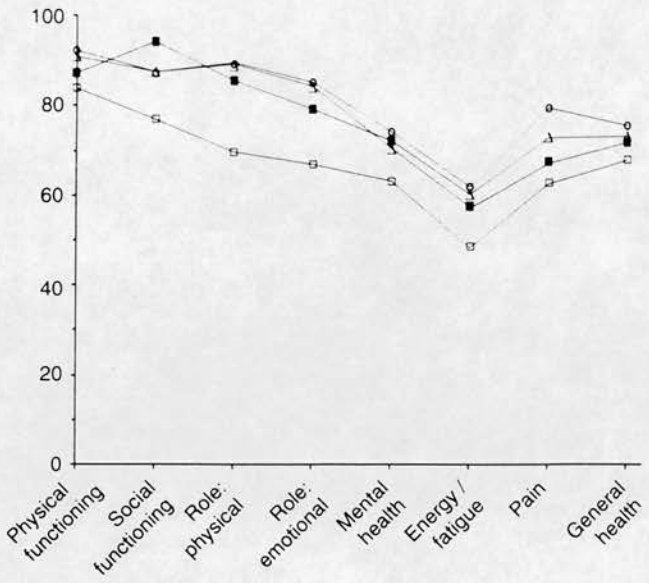

Fig. 3. Follow up Short Form 36 scores. ■ = prefers medical; □ = randomised medical; Δ = prefers TCRE; ○ = randomised TCRE.

controlled trial group. This represented about a 40% relative increase. It was not associated with any increase in drop-outs. The difference in overall participation was entirely explained by those who agreed to join one of the preference groups. Making the option of preferred management more explicit did not therefore appear to reduce the number who agreed to allow their treatment to be chosen by random allocation, and this was reinforced by the finding of similar reasons for not agreeing to randomisation in the two trial design groups. Nevertheless, the confidence interval around our estimate (−15% to 7%) is too wide to rule out an important difference in this respect. Our rate of expressed preference (30%) is similar to that described by Coulter *et al.*[12].

There were systematic differences at the start of the study between the preference groups and those who agreed to be randomised. Women who chose medical management tended to have better general health, were less restricted by their menstrual problems, and fewer had been treated previously by their general practitioner. Those who chose TCRE had all tried medical management, had higher bleeding and pain scores, and had a greater desire for amenorrhoea. The randomised comparison involved women who were prepared to accept either management and they tended to fall between the preference groups in terms of their menstrual history. There was, however, no evidence that making the option of preference more explicit influenced recruitment to the trial. A conventional randomised controlled trial in this context would not therefore be biased by motivational factors.

Figure 3 shows that the follow up Short Form 36 scores were highest in the two groups managed with TCRE but not clearly different from the preferred medical group. Satisfaction levels were lower in the preferred medical group than in the two TCRE groups. The appearance in Fig. 3 that the Short Form 36 scores of the preferred medical group were clearly better that the randomised medical group is potentially misleading because it reflects the marked differences at baseline (Fig. 2). There was relatively little scope for the preferred medical group's scores to improve and in fact the changes in scores were greater in the randomised medical management group (Table 5). On the basis of these results, despite TCRE performing better in the randomised comparison, it is clearly reasonable to manage women medically who wish to avoid surgery, while recognising that outcome following medical management may be suboptimal even in this group.

Satisfaction was lower in the preferred TCRE group than following randomised TCRE. This may reflect the higher expectations in the preferred group (Table 3). Specifically, some of these women expressed disappointment in not achieving amenorrhoea; arguably hysterectomy should be considered for these women.

We found that the additional 40% of participants in the PRPP design represented a very significant extra workload; we also found the interpretation of the results of the preference groups much more difficult because they were based on observational comparisons. Information on the number and characteristics of eligible patients who are not entered into randomised clinical trial is considered important by some in the assessment of generalisability[3,17,18] and this is potentially the major contribution of the preference groups in this study. Although the finding that women who preferred medical management were less severely affected and had received less prior treatment underscored the need to extrapolate the findings of the randomised comparison prudently, this would, anyway be a sensible conclusion from the results of the randomised comparison alone. Obviously it is good practice to support women who wish to avoid surgery and who choose to try medical management. In respect of surgical management, those who preferred TCRE tended to be less satisfied than those randomised to it. Again, however, this would not be surprising if women hoped for amenorrhoea. It would be good clinical practice to clarify women's expectations, and if amenorrhoea is important to a woman to discuss hysterectomy as one of the possible options.

Data from the preference groups in this study thus tends to confirm conclusions that follow from the randomised comparison. The resource implications of getting this extra information are significant, however. Given that randomised comparisons are often too small to give reliable answers, these resources may be better used to increase recruitment to a randomised compari-

son to ensure more robust results. In a situation in which there is concern that motivational factors may introduce bias into a randomised comparison, the most efficient way to address this may be by recording any preference at trial entry and then examining in the analysis whether preference does modify any differential effects[19].

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A randomised comparison of medical and hysteroscopic management in women consulting a gynaecologist for treatment of heavy menstrual loss

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Objectives To compare medical with hysteroscopic management in women referred to a gynaecologist complaining of heavy menstrual loss.

Design Single-centre randomised trial.

Setting A teaching hospital in the United Kingdom.

Participants One hundred and ninety-seven women seeking specialist treatment of heavy menstrual loss for the first time and willing to accept either treatment.

Interventions 1. Medical treatments not previously used by the women prescribed by experienced gynaecologists in standard doses and timings for a minimum of three cycles (n = 94), and 2. transcervical resection of the endometrium performed under general anaesthesia five weeks after goserelin preparation (n = 93).

Main outcome measures Treatment satisfaction and acceptability, relief of symptoms, change in haemoglobin, and improvement in health related quality of life, all after four months.

Results Women allocated transcervical resection were more likely to be totally or generally satisfied (76% *versus* 27%, $P < 0{\cdot}001$), to find the treatment acceptable (93% *versus* 36%, $P < 0{\cdot}001$), and willing to have the treatment again (93% *versus* 31%, $P < 0{\cdot}001$). Although pain and bleeding were significantly reduced by medical treatment this was modest in comparison with transcervical resection ($P < 0{\cdot}001$). Haemoglobin levels were significantly increased only following transcervical resection. Short form 36 scores were also improved in both arms, although only transcervical resection returned them to normal values.

Conclusions Medical treatment was less effective than transcervical resection of the endometrium, irrespective of previous treatment or type of medical management. Early hysteroscopic endometrial surgery should be considered by such woman with the choice made by the woman after a full discussion of the advantages and disadvantages of all the options.

INTRODUCTION

Heavy menstrual loss is a common complaint accounting for about 12% of all referrals to gynaecology outpatient departments[1]. Many of these women are initially prescribed medical treatments by gynaecologists; these are known to reduce blood loss in a significant proportion of women with objectively proven menorrhagia[2–8]. Among those seeking surgery, hysteroscopic techniques for endometrial ablation, such as transcervical resection of the endometrium, have been shown to be effective, achieving high rates of patient satisfaction[9–12]. At present it is recommended that these techniques are offered as an alternative to hysterectomy after medical managements have failed[11]. We undertook this pragmatic[13] randomised comparison of medical treatment with transcervical resection of the endometrium to clarify the place of hysteroscopic surgery in the management of women when first referred to a gynaecologist with heavy menstrual loss. The women who participated were equally willing to accept medical or hysteroscopic management.

METHODS

With local research ethics committee approval, women were recruited from the general gynaecology clinics of 9 of the 11 consultants at this large teaching hospital between October 1994 and September 1995. They were

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eligible if consulting a gynaecologist for the first time with a complaint of heavy menstrual loss, their family was complete, they had a clinical diagnosis of dysfunctional uterine bleeding (uterus less than ten weeks pregnancy size and normal endometrial pathology) and had not been referred specifically for surgery. They also had to be willing to be randomised to either medical or hysteroscopic management.

After giving informed consent, a clinical questionnaire, the hospital anxiety and depression scale[14], and Short Form 36[15,16] were completed, and blood was taken for haemoglobin estimation. Bleeding and pain scores were determined by assigning a score from zero to five for heaviness of bleeding or severity of pain for each menstrual day, for a maximum of 10 days. These measurements, except for the hospital anxiety and depression scale, were repeated four months after starting treatment to assess outcome. Satisfaction, acceptability (using direct questioning and by Semantic Differential Technique[17]), and preferred subsequent treatment were also ascertained then.

Women were randomly allocated to either 'transcervical resection' or 'medical treatment' by opening sealed, serially numbered, opaque envelopes; the order was determined by computer generated random numbers within balanced blocks of twenty. The actual choice of medical treatment, which should not have been used by the patient before as treatment for heavy menstrual loss was selected by the senior gynaecologist responsible for the clinic and continued for at least three cycles.

Women allocated surgery received an injection of the gonadotrophin releasing hormone analogue, goserelin 3·6 mg. Five weeks later they were admitted under the care of one of the three participating gynaecologists who performed hysteroscopic surgery. Transcervical resection of the endometrium was performed under general anaesthesia using rollerball coagulation to the fundus and cornua with resection of the cavity walls using a 90°, 7 mm diameter loop, with 1·5% glycine solution as the distending medium.

Based on expected satisfaction rates of approximately 80% at four to six months after transcervical resection of the endometrium[9–11] it was calculated that a minimum of 180 women would be required to have 80% power to detect an absolute difference of 20% at the 5% level of significance[18]. Analysis was by intention-to-treat. Independent and paired *t* tests were used for continuous variables (independent and related) with a normal distribution and the Mann-Whitney *U* test for ordinal or non parametric continuous variables. The χ^2 test was used for independent nominal data and McNemars test for paired data describing dichotomous variables. Secondary analyses were stratified according to the number of medical treatments used prior to gynaecological referral.

Table 1. Baseline characteristics of each randomised group at recruitment. Values are given as *n* (%) of women, mean [SD] or mean score with {95% CI} below. TCRE = transcervical resection of the endometrium; HADS = hospital anxiety and depression scale.

	Randomised	
	Medical ($n = 94$)	TCRE ($n = 93$)
Mean age	41·4 [5·2]	41·7 [5·2]
Mean haemoglobin (g/dL)	12·79 [1·19]	12·65 [1·63]
Menstrual symptoms		
Irregular periods	49 (52)	52 (56)
3–5 days bleeding	15 (16)	11 (12)
>5 days bleeding	79 (84)	82 (88)
No. days heavy bleeding	4·56 [2·35]	4·28 [2·22]
Regular dysmenorrhoea	53 (56)	48 (52)
Menstrual symptom rating scale		
Mild or moderate	1 (1)	0 (0)
Severe	59 (63)	53 (58)
Very severe	28 (30)	36 (39)
Bleeding score	24·2 [8·5]	25·0 [7·6]
Pain score	14·7 [9·5]	13·5 [10·7]
Premenstrual symptoms		
Bloating	71 (76)	75 (82)
Breast discomfort	65 (70)	65 (71)
Irritability	65 (70)	68 (75)
Headaches	63 (68)	54 (59)
Depression	53 (57)	51 (56)
HADS		
Anxiety	8·96 {7·8–10·1}	8·85 {7·6–10·1}
Depression	5·62 {4·7–6·6}	5·31 {4·3–6·5}

RESULTS

One hundred and eighty-seven of 273 eligible women (69%) consented to randomisation, 94 were allocated to medical treatment and 93 to transcervical resection. The majority of those who refused randomisation had a preference for one or other treatment. The results for these women are described in the accompanying paper. All women but one were assessed at follow up at an average of nineteen weeks following TCRE or starting medication.

Patient characteristics

The participants are described in Table 1; the trial groups had similar expectations of treatment and were also of equivalent height, weight and social status. Almost 80% in each group were employed with about 30% requiring time off work because of menstrual symptoms. Similar numbers had heavy menstrual flow for more than one year (78% and 84%, respectively) while 24/82 women (29%) in the medical arm and 22/85 (26%) in the surgical arm had haemoglobin levels of less than 12 g/dL. Baseline Short Form 36 scores

Table 2. Short form 36 health survey questionnaire mean baseline scores and change in score at four month follow up. Scores range from 0 to 100 (worst to best). Values are given as mean [SD]. Key as for Table 1.

Short Form 36	Medical ($n = 93$)	TCRE ($n = 93$)	P
Baseline scores			
Physical functioning	78·88 [20·72]	81·94 [19·38]	0·30
Social functioning	69·10 [20·98]	69·06 [24·29]	0·99
Role			
Physical	54·26 [37·86]	56·72 [39·38]	0·66
Emotional	57·80 [42·10]	53·41 [44·00]	0·49
Mental health	58·32 [18·27]	59·14 [19·08]	0·77
Energy/fatigue	41·24 [16·84]	41·51 [19·22]	0·92
Pain	53·8 [24·84]	57·95 [25·16]	0·26
General health	68·02 [18·85]	65·10 [20·05]	0·31
Change in score			
Physical functioning	4·84* [16·72]	10·16† [16·51]	< 0·05
Social functioning	7·57* [26·26]	17·44† [25·08]	< 0·05
Role			
Physical	15·32* [46·78]	32·26† [38·23]	< 0·01
Emotional	8·96* [49·43]	31·54† [45·94]	< 0·01
Mental health	4·78* [16·69]	15·01† [19·00]	< 0·01
Energy/fatigue	7·07* [20·23]	20·53† [20·76]	< 0·01
Pain	8·84* [26·39]	21·62† [31·33]	< 0·01
General health	−0·25 [15·99]	10·49† [20·85]	< 0·01

Footnote marks denote significant changes from the baseline: *$P < 0·05$, †$P < 0·01$.

were also comparable for each group (Table 2). 22% of women had received no previous medical treatment, 56% one, and 22% two different treatments, from their general practitioner. 60% of women in both arms reported self treatment with analgesics perimenstrually. Overall, baseline anxiety scores were elevated (8·96 and 8·85) whereas depression scores were in the normal range (5·62 and 5·32)[14,19].

Medical treatment

Table 3 shows the actual treatment prescribed to the medical group. Progestogens were prescribed from day 12–25, or 5–25 if there was also dysmenorrhoea. The combined oral contraceptive pill preparations recommended were second generation containing 30 μg oestradiol. Tranexamic acid was prescribed at a dose of 1 g four times a day for the first five days of the period in women with regular periods, with mefenemic acid 500 mg three times a day added if there was associated dysmenorrhoea. Danazol was prescribed at a dose of 200 mg per day continuously for 90 days. No women received a treatment that she had previously tried. Only women with heavy and irregular periods received progestogens. Eighty percent of women reported completing the treatment as prescribed, 9% occasionally missing tablets, and 11% stopping medication prior to follow up. There was no significant difference in satisfaction or

Table 3. Drug treatments received by those randomised to medical treatment, and rates of satisfaction, acceptability and desire to continue the same treatment at follow up. Values are given as n (%) of women. Progestogens day 5–25 = 22/31 women, 12–25 = 9/31 women. HRT= hormone replacement therapy, NSAID= non steroidal anti-inflammatory drug

		Treatment		
	$n = 94$	Satisfactory	Acceptable	Continue
Progestogens day 12–25 / 5–25	31 (33)	10 (34)	11 (36)	6 (19)
Combined pill	24 (26)	8 (33)	8 (33)	6 (25)
Tranexamic acid	22 (23)	7 (34)	6 (29)	4 (18)
Danazol	15 (16)	5 (33)	7 (47)	3 (20)
HRT (with NSAID)	2 (2)	1 (50)	1 (50)	2 (100)

acceptability rates between the medical treatments used (Table 3). One woman underwent transcervical resection after continual bleeding for two months on her allocated medical treatment.

Transcervical resection of the endometrium

All those allocated transcervical resection were initially managed this way. The only operative complication was persistent uterine bleeding which occurred in six women. This abated in all cases following the insertion of a uterine foley catheter at the end of the procedure with removal six hours later. One woman had a two stage hysteroscopic procedure and one woman later had a hysterectomy, both because of submucous fibroids.

Menstrual status at follow up

Transcervical resection of the endometrium reduced bleeding and dysmenorrhoea significantly better than medical treatment (Table 4, $P < 0·001$ for all variables) and achieved amenorrhoea in 37%. Although the number of heavy days, and bleeding and pain scores, were significantly reduced by medical therapy the effect size was significantly smaller than after surgery. This was reflected in changes in mean haemoglobin levels. Medical treatment did not significantly improve any of the five premenstrual symptoms, whereas all were significantly improved following transcervical resection.

Satisfaction/acceptability

Transcervical resection resulted in significantly greater levels of satisfaction, symptom improvement and acceptability (Table 5). Semantic differential rating scores were better on all parameters for hysteroscopic surgery and significantly so for all except pain (Table 6). The most common reason for dissatisfaction with

Table 4. Menstrual status and symptoms at 4 months follow up. Values are given as *n* (%) of women or mean [SD]. TCRE = transcervical resection of the endometrium; Hb = haemoglobin (medical: $n = 82$ [< 12 g/dL: $n = 24$], TCRE: $n = 85$ [< 12 g/dL: $n = 22$]); 95% CI = 95% confidence intervals for difference in means or proportions (%).

	Randomised medical ($n = 93$)	Randomised TCRE ($n = 93$)	95% CI	*P*
Mean increase in Hb level (g/dL)	0·18 [1·29]	0·76‡ [1·62]	−1·04 to −0·12	0·014
Mean increase in Hb if baseline <12 g/dL	0·93† [1·5]	2·53‡ [1·94]	−2·64 to −0·56	0·003
Menstrual status				
Unchanged or heavier	48 (52)	7 (8)	33 to 56	<0·001
Duration of bleed				
None	3 (3)	34 (37)		
< 3 days	3 (3)	17 (18)	37 to 59	<0·001
3–5 days	29 (31)	24 (26)		
> 5 days	58 (62)	17 (18)		
No. of days heavy bleeding	3·15‡ [2·8]	0·76‡ [1·3]	1·75 to 3·03	<0·001
Bleeding score	17·8‡ [9·15]	5·1‡ [6·97]	10·25 to 15·29	<0·001
Pain score	9·7‡ [8·92]	2·8‡ [6·14]	4·51 to 9·24	<0·001
Dysmenorrhoea—same or worse	42 (46)	14 (15)	18 to 53	<0·001
Premenstrual symptoms				
Breast discomfort	55 (60)	40‡ (44)	2 to 31	0·03
Bloating	73 (79)	53‡ (58)	8 to 35	0·002
Irritability	62 (67)	49† (54)	1 to 28	0·06
Headaches	57 (62)	34† (37)	11 to 39	<0·001
Depression	51 (55)	21‡ (23)	19 to 46	<0·001

Footnote marks denote changes from baseline: *$P < 0·05$, †$P < 0·01$, ‡$P < 0·001$.

medical treatments was no change in the severity of bleeding or pain, although 'bad side effects' were cited by twenty seven (45%) of the sixty women who found treatment unacceptable. A total of forty six (48%) in the medical arm and twelve (13%) in the transcervical resection arm reported symptoms which they considered to be side effects, specifically nausea, headaches and weight gain in the medical group and new pain equally in both groups. One woman prescribed danazol suffered a cerebro-vascular accident two months into treatment, while another developed hypertension which resolved on stopping the combined pill.

Health related quality of life

There was significantly greater improvement in all eight subscales of the Short Form 36 following transcervical resection (Table 2). The number of women requiring time off work each month in the medical arm (29%) did not change with treatment, but was significantly reduced ($P < 0·001$), in the surgical cohort (6%).

Secondary analysis stratified by previous medical management

Outcome in respect of bleeding and pain scores, menstrual symptoms, satisfaction, and acceptability was significantly better among women allocated hysteroscopic management in all strata characterised by the number of previous medical treatments, including the 22% who had not previously had medical treatment.

DISCUSSION

The results of the hysteroscopic surgery group are clearly better than those of the medically managed group. But are the results trustworthy and if so to whom do they apply?

Bias between the two study groups in the way that they were selected, if it exists, is likely to be small; the groups were randomly allocated, there was only one loss to follow up, and the groups were similar at entry (Table 1). We used established and recognised questionnaires measuring clinical and quality of life parameters, satisfaction and acceptability of treatment[9,14–17,20,21]. We recognise that these are subjective. To minimise ascertainment bias, we limited participation in the trial to women who were willing to accept either management. Those who would not accept randomisation were studied separately and are discussed in the accompanying paper. We know that some commentators will argue that the optimal medical treatments might not have been used for each patient and that significant reduction in menstrual blood loss only occurs when the original loss is objectively pathological. In this pragmatic[13] trial experienced clinicians prescribed what they regarded to be the most appropriate standard medical treatment for each woman based on their findings at consultation (Table 3). The individual drug therapies were prescribed in doses and timing used in studies demonstrating the effectiveness of these medications and as recommended by the British National Formulary[2–8,22]. We would emphasise that 22/31 women prescribed progestogens had these from days 5 to 25 which has been shown to

Table 5. Patient satisfaction, menstrual symptom rating scale, effectiveness and acceptability of treatment and desired future treatment. Values are given as *n* (%) of women. 95% CI = 95% confidence interval for difference in proportion (%).

	Randomised medical ($n = 93$)	Randomised TCRE ($n = 93$)	95% CI	*P*
Totally or generally satisfied with treatment	25 (27)	70 (76)	−61 to −36	< 0·001
Cure or acceptable improvement in symptoms	29 (32)	77 (85)	−64 to −40	< 0·001
Menstrual symptom rating scale				
None	2 (2)	34 (37)	−45 to −24	< 0·001
Mild or moderate	39 (42)	51 (53)		
Severe	42 (45)	6 (6)		
Very severe	10 (11)	1 (1)		
Treatment acceptable	33 (35)	85 (91)	−67 to −45	< 0·001
Prepared to have same treatment again	29 (31)	86 (92)	−72 to −51	< 0·001
Would recommend the treatment	38 (41)	84 (90)	−61 to −38	< 0·001
Did not require days off work	56 (71)	73 (94)	−31 to −5	< 0·001
Treatment desired				
None	3 (3)	82 (88)	−92 to −78	< 0·001
Medical (same or different)	40 (43)	5 (5)		
TCRE	49 (53)	2 (2)		
Hysterectomy	1 (1)	4 (4)		

Table 6. Semantic differential rating scores for acceptability of treatment (score −3 [best] to −3 [worst]). Values are given as mean [SD]. 95% CI = 95% confidence interval for difference in mean.

Adjectival pair	Medical ($n = 93$)	TCRE ($n = 93$)	95% CI	*P*
Painless–painful	−0·44 [1·74]	−0·71 [1·79]	−0·25–0·78	0·3
Happy–sad	−0·12 [1·56]	−1·42 [1·43]	0·87–1·74	< 0·001
Pleasant–unpleasant	0·11 [1·55]	−0·58 [1·33]	0·27–1·10	0·002
Positive–negative	−0·14 [1·81]	−1·80 [1·44]	1·19–2·14	< 0·001
Safe–dangerous	−0·68 [1·65]	−1·75 [1·21]	0·65–1·49	< 0·001
Attractive–unattractive	0·01 [1·04]	−0·40 [0·89]	0·13–0·69	0·004
Mild–harsh	−0·52 [1·41]	−1·12 [1·32]	0·21–1·00	0·003
Agreeable–disagreeable	−0·23 [1·92]	−1·30 [1·39]	0·59–1·57	< 0·001
Active–passive	−0·23 [1·12]	−0·77 [1·24]	0·20–0·89	0·002
Easy–hard	−1·01 [1·79]	−1·58 [1·41]	0·11–1·04	0·016
Fast–slow	−0·23 [1·69]	−1·69 [1·35]	0·88–1·77	< 0·001
Good–bad	0·02 [2·03]	−2·09 [1·34]	1·61–2·61	< 0·001

significantly reduce menstrual blood loss[8,22]. More specifically no women received progestogens in a dose or timing previously shown to be of little use in the management of menorrhagia. Furthermore, the trial results consistently favoured hysteroscopic management, irrespective of the type of medical treatment prescribed by the gynaecologist or whether medical treatment had previously been tried or not. Also, satisfaction, acceptability and willingness to continue the same treatment were similar for all the medical treatments used (Table 3) (although we acknowledge these were not randomly allocated). We recognise that some women in the medical arm, as in the surgical group, may have had fibroids that were not detected on clinical examination or endometrial biopsy and which might not have responded to medical treatment.

Although the medically managed group showed improvement at follow up this was consistently less than in the resection group. This applied to all assessments of menstrual status, including premenstrual symptoms and dysmenorrhoea (Table 4). Premenstrual symptoms have previously been shown to improve following endometrial ablation[9,23]. Satisfaction and acceptability were also clearly higher in the transcervical resection group (Tables 5 and 6), and this was reflected in the numbers of women who would have the same treatment again, would recommend it to another person, and desired further treatment. Transcervical resection of the endometrium achieved satisfaction and acceptability rates which were comparable to those obtained in previous randomised trials[9,10,12], even though women in this trial were not specifically seeking surgical treatment.

Heavy menstrual loss is known to cause significant deterioration in general health and quality of life[21,24–25] which has often been overlooked in the assessment of treatment. The reduced Short Form 36 scores observed at baseline were consistent with the scores reported for other women with menorrhagia[25]. After medical

treatment there were significant improvements in all parameters except for general health, but normal scores were not attained for any of the eight parameters. In contrast, scores equal to or better than normal for all eight Short Form 36 scales were observed after transcervical resection (Table 2)[20]. This concurs with the findings of Coulter and colleagues[26].

Objective measurement of blood loss was not undertaken as this is not yet routine clinical practice. An assessment of severity of menstrual loss and treatment success was undertaken by measuring haemoglobin level at recruitment and follow up. The significantly greater mean increase in haemoglobin concentration among women allocated transcervical resection is consistent with the differences in the subjective measures of outcome.

It is noteworthy that 48% of women in the medical arm reported side effects and over half deemed these unacceptable. None of the six surgical complications was serious. However, these women did undergo a general anaesthetic and we recognise that significant risks of hysteroscopic surgery exist, but are too uncommon to evaluate reliably in a trial of this size.

These results should be generalisable to women first seeking advice from a gynaecologist for management of heavy menstrual bleeding who have no treatment preference. Seventy percent of those fulfilling the entry criteria agreed to randomisation. In the accompanying report we describe the results for those who refused randomisation who had a preference for transcervical resection or medical treatment in equal proportions. Those who had a preference for medical management (and so were not randomised) fared better than those randomised to medical treatment, but their results were still not as satisfactory as those following transcervical resection.

A formal economic evaluation was not conducted. The cost of hysteroscopic surgery has been estimated at £560[27] which will be offset to some extent by the costs of medical management. However, the resource implications of introducing transcervical resection of the endometrium to all gynaecological centres and the training requirements involved could be considerable, and these would need to be included in any assessment of cost-effectiveness. Also, new, technically less demanding ablative techniques that can be undertaken using local anaesthesia have recently been reported[28–30], while the progestogen loaded coil seems effective in reducing menstrual loss[22,31]. A more conservative approach could be adopted through reassurance and counselling for those determined to have menstrual loss within normal limits. All these methods of management require formal evaluation in randomised controlled trials before accepting them as effective advances in the management of women complaining of heavy menses. Also, those who believe that the medical management tested in this trial was sub-optimal should test this assumption in further rigorous trials against endometrial ablative surgery.

In the meantime, this trial indicates that early ablative surgery should be one of the options considered by women consulting a gynaecologist for the first time seeking treatment of excessive menstrual loss, with the choice made by her after a full discussion of the advantages and disadvantages of all the various treatment options.

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Two-year follow up of women randomised to medical management or transcervical resection of the endometrium for heavy menstrual loss: clinical and quality of life outcomes

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Objective To assess clinical status and changes in health related quality of life after two years in women randomised to medical management or transcervical resection of the endometrium (TCRE) for treatment of heavy menstrual loss.

Design Two-year follow up using postal questionnaires and operative databank review.

Setting Gynaecology department of a large UK teaching hospital.

Participants Women who had joined a randomised comparison of medical treatment with TCRE for heavy menstrual loss two years previously.

Main outcome measures Women's satisfaction with treatment, gynaecological symptoms, changes in health related quality of life, and additional treatments received at two years.

Results Women allocated medical treatment were significantly less likely to be totally or generally satisfied (57% *vs* 79%, difference −22%, 95% CI −36, −9%), to find their management acceptable (77% *vs* 93%, difference −16%, 95% CI −26, −4%), or to recommend their allocated treatment (24% *vs* 78%, difference −54%, 95% CI −61, −33%). In the medical cohort 59% of women had undergone TCRE, hysterectomy or both, whereas 17% in the TCRE cohort had undergone further surgery. Bleeding and pain scores were similar in the groups and highly significantly better than at recruitment. Short Form-36 health survey scores were significantly improved from baseline for five of the eight health scores in the medical arm, and seven in the TCRE arm.

Conclusions The results at two years consolidate the findings and conclusions based on the four-month follow up data. A policy of early TCRE is effective and safe and does not result in an increase in hysterectomies. It should not be routinely withheld in an effort to try alternative medical therapies.

INTRODUCTION

Medium and long term follow up data are now available for hysteroscopic endometrial ablative techniques for women who would otherwise have undergone hysterectomy[1–3]. In contrast, there is a paucity of follow up data of longer than six months for women prescribed medical treatment for menorrhagia[4], and there is evidence that problematic menses recur on cessation of therapy[5,6]. The majority of trials assessing medical treatments also adopt an explanatory, rather than pragmatic approach to investigation[7,8], the emphasis being on reduction in measured menstrual blood loss in women with proven pathological loss (> 80 mL/cycle), who represent less than half of all women complaining of heavy menstrual loss[9,10] and of those referred for endometrial ablation[11]. Few studies have assessed satisfaction with treatment or the women's desire to continue the same treatment. More importantly, no other studies have evaluated the effect of medical treatments on health related quality of life, despite strong evidence that women complaining of heavy periods suffer a significant reduction in this[12–14].

We have reported[14] the short term results of this randomised trial comparing medical treatment with TCRE for women attending a gynaecologist for the first time for treatment of heavy menstrual loss. The trial involved women who were not specifically referred for

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surgical treatment and who were equally prepared to have medical treatment or TCRE[15]. The present report is a description of the two-year follow up of these women, re-evaluating their outcomes with respect to subsequent treatments received, satisfaction with and acceptability of treatment, and change in health related quality of life.

METHODS

Full details of the original trial design, treatment allocation, and outcome measures at four months have been reported previously[14]. In summary, women were eligible if they met the following entry criteria: consulting a gynaecologist for the first time with a complaint of heavy menstrual loss; family complete; a clinical diagnosis of dysfunctional uterine bleeding (uterus < 10 weeks of pregnancy size and normal endometrial pathology); and had not been referred specifically for surgery. They also had to have no preference for either medical or hysteroscopic management. Of 272 eligible women, 187 (69%) consented to randomisation, 94 being allocated to medical treatment and 93 to transcervical resection. The majority of those who refused randomisation had expressed a preference for one or other treatment and were evaluated separately[15]. After follow up at four months, all recruits, irrespective of initial management, could request further and/or different treatment. This policy reflected normal clinical practice in keeping with the pragmatic design of the trial.

Postal questionnaires were sent two years after initial treatment, assessing gynaecological symptoms, satisfaction with treatment, and acceptability of management. Changes in health related quality of life were measured using the Short Form-36 health survey (SF-36)[16,17]. Subsequent treatments were also determined, both from the questionnaire and from the hospital surgical database. As this is the only hospital with a gynaecological service for the district, we can be certain of further hospital treatment received for those who had not left the Grampian region of Scotland.

The original sample size calculations indicated that 180 women would be the minimum number required for the study to have 80% power to detect an absolute difference in satisfaction with treatment of 20% at the 5% level of significance[18]. Analysis was by intention-to-treat: that is, women remained in the group to which they were originally allocated, irrespective of subsequent treatment. *t* tests were used for variables with a normal distribution, using the non-paired version for independent comparisons and the paired version otherwise. Similarly the Mann-Whitney *U* test and the paired Wilcoxon signed rank test were used for non-parametric data. Independent nominal data were analysed using either the χ^2 test or Fisher's exact test, depending on sample size. McNemar's test was used for paired dichotomous data.

RESULTS

One hundred and eighty-seven women were originally recruited between October 1994 and November 1995. 94 randomised to have medical treatment and 93 to TCRE. Postal follow up questionnaires two years (range 23 to 28 months) after initial treatment were completed by 173 (92%) women, 86 in the medical group and 87 in the TCRE group. Six of the 14 not followed up were known to have left the region.

Participants

Table 1 summarises the baseline characteristics of those successfully followed up: they were very similar to the total trial group[14]. At the time of recruitment almost 80% in each group were employed, with about 30% requiring time off work because of menstrual symptoms. Similar numbers had heavy menstrual flow for more than one year (78% and 84%, respectively). Hospital Anxiety and Depression Scale anxiety scores were elevated (9·35 and 8·78), whereas depression scores were in the normal range (5·76 and 5·29)[19]. Baseline SF-36 scores were also comparable for each group and globally reduced relative to women of the same age in the general population[20] (Table 2 and Fig. 1). Complete details, have already been reported[14], and a reminder of the actual medical treatment allocated and stratified results at four months is given in Table 3.

Subsequent treatment received or continued at two years

Subsequent management is summarised in Table 4. At two-year follow up, 59% of those randomised to medical treatment had undergone TCRE, hysterectomy or both; 82% of the initial operations had been undertaken within 12 months of trial entry. Twenty percent of the women remained on medical treatment, although specific medications were not determined. 17% of women allocated to TCRE had undergone repeat TCRE, hysterectomy or both. One hysterectomy, in the TCRE arm, resulted from an emergency laparotomy performed for acute sepsis and generalised peritonitis, secondary to bilateral rupture of pyosalpinges in an amenorrhoeic woman 14 months after initial TCRE. No women requested further surgery or medication after completing the questionnaire. Operative data were obtained from the hospital surgical database for the fourteen participants who did not complete two-year questionnaires. Of eight women in the medical arm, four had undergone TCRE; among six in the TCRE arm, one hysterectomy had been performed.

Table 1. Baseline characteristics of each randomised group at recruitment. Values are given as *n* (%) of women or mean [SD] unless otherwise indicated. TCRE = transcervical resection of the endometrium.

	Randomised medical ($n = 86$)	Randomised TCRE ($n = 87$)
Age (years)	41·4 [5·4]	41·9 [5·1]
Haemoglobin (g/dL)	12·79 [1·16]	12·61 [1·66]
Menstrual symptoms		
Irregular periods	45 (52)	49 (58)
3–5 days bleeding	14 (16)	9 (11)
> 5 days bleeding	72 (84)	78 (89)
No. of days heavy bleeding	4·6 [2·43]	4·24 [2·19]
Regular dysmenorrhoea	53 (56)	48 (52)
Menstrual symptom rating scale		
Mild or moderate	6 (7)	4 (4)
Severe	54 (63)	51 (59)
Very severe	26 (30)	32 (37)
Bleeding score	24·7 [8·6]	24·8 [7·3]
Pain score	15·2 [9·6]	13·3 [10·2]
Premenstrual symptoms		
Bloating	64 (75)	70 (82)
Breast discomfort	60 (71)	63 (74)
Irritability	60 (71)	64 (75)
Headaches	57 (67)	57 (61)
Depression	49 (58)	50 (59)
Hospital Anxiety and Depression Scale		
Anxiety: mean score (95% CI)	9·35 (8·47 to 10·22)	8·78 (7·85 to 9·70)
Depression: mean score (95% CI)	5·76 (5·06 to 6·45)	5·29 (4·54 to 6·05)

Menstrual status at follow up

Changes in menstrual symptoms at two years are shown in Table 5. There was a highly significant and comparable reduction in bleeding and pain scores in both trial groups. Similar numbers in both cohorts reported no new pelvic pain of any kind (60% medical, 64% TCRE, $P = 0·44$). Significantly fewer women in the medical arm were

Table 2. Short Form-36 Health Survey Questionnaire: mean (SD) baseline scores and change in score at two-year follow up. Scores range from 0 → 100 (worst → best).

	Medical ($n = 83$)	TCRE ($n = 86$)	Actual difference	P	95% CI
Short Form-36: baseline scores					
Physical functioning	78·67 (21·14)	82·33 (18·56)	−3·66	0·23	−9·7 to 2·4
Social functioning	68·35 (21·04)	70·03 (24·05)	−1·68	0·63	−8·5 to 5·2
Role: physical	53·01 (38·33)	56·98 (39·23)	−3·97	0·51	−15·7 to 7·8
Role: emotional	57·43 (43·03)	55·03 (43·62)	2·40	0·72	−10·8 to 15·6
Mental health	58·20 (18·23)	59·43 (18·97)	−1·23	0·67	−6·9 to 4·5
Energy/fatigue	40·36 (17·17)	41·49 (19·15)	−1·13	0·69	−6·7 to 4·5
Pain	53·55 (23·99)	58·14 (25·15)	−4·59	0·23	−12·1 to 2·9
General health	68·17 (19·00)	65·90 (19·34)	2·27	0·45	−3·6 to 8·1
Short Form-36: change in score					
Physical functioning	3·73 (17·19)	5·00 (18·97)*	−1·27	0·65	−6·4 to 4·2
Social functioning	3·94 (25·26)	10·59 (26·52)	−6·65	0·10	−14·5 to 1·2
Role: physical	12·95 (44·58)**	18·60 (45·73)	−5·65	0·42	−19·4 to 8·1
Role: emotional	11·25 (45·17)*	22·48 (50·47)	−11·23	0·13	−25·8 to 3·3
Mental health	7·17 (19·20)	9·98 (19·14)	−2·81	0·35	−8·7 to 3·1
Energy/fatigue	10·06 (19·57)	14·58 (21·96)	−4·52	0·17	−11·0 to 2·0
Pain	11·38 (28·51)	12·34 (27·20)	−0·96	0·82	−9·4 to 7·5
General health	−0·67 (13·90)	1·69 (18·83)	−0·97	0·36	−7·4 to 2·7

Follow up statistical comparisons between trial groups are for change in score.
Asterisks/daggers denote significant changes in score from the baseline (*$P < 0·05$, **$P < 0·01$, $P < 0·001$).

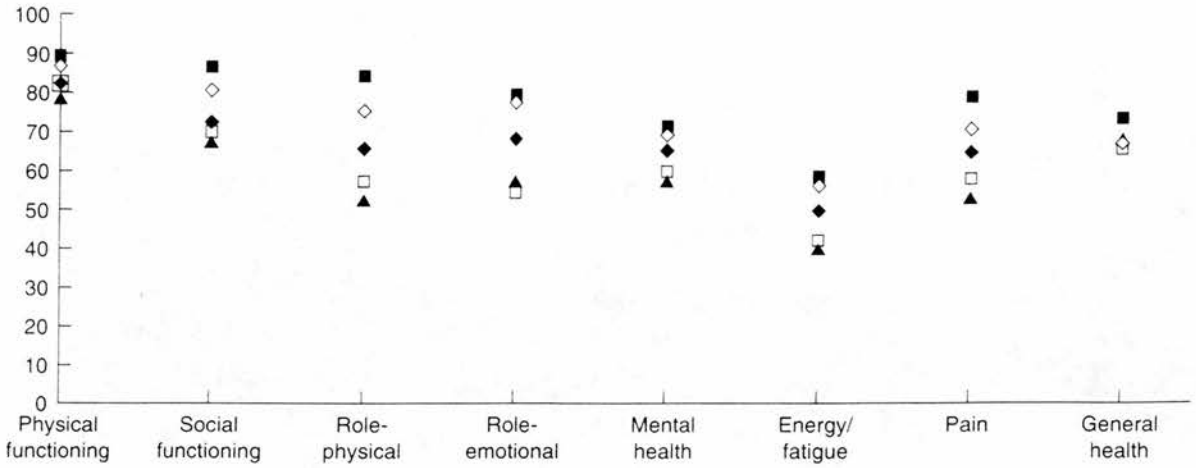

Fig. 1. Short Form-36 scores. ▲ baseline medical; □ baseline TCRE; ■ normative values; ◆ 24 month medical; ◇ 24 month TCRE.

amenorrhoeic or had very light periods (spotting / bleeding score from 1 to 5), than in the TCRE arm (44% compared with 60%), while significantly more women in the medical arm regarded their menstrual status as unchanged or worse (18% compared with 6%). Significant reductions were present in three of the five premenstrual symptoms in the medical arm, whereas no significant differences had been detected at four months. Significant reductions in all five premenstrual symptoms in the TCRE arm were evident, but with the exception of headaches and irritability, these benefits were less than at four months. Overall there was no significant difference in premenstrual symptoms between the two study groups.

Satisfaction/acceptability

Compared with the medical group, women allocated TCRE had significantly higher levels of satisfaction and symptom improvement. They were also more likely to find their treatment acceptable (Table 6). These values were much improved in the medical arm from the four month data, whereas those for TCRE were similar. Only 24% of women allocated to medical treatment would recommend this form of treatment, compared with 78% in the surgical arm who would recommend TCRE ($P < 0{\cdot}001$, difference −54%, 95% CI −66% to −44%). Of the 47 women in the medical arm who underwent a TCRE, 40 (85%) of them would recommend this form of treatment.

Health related quality of life

Baseline and two-year SF-36 follow up data are presented for women who had completed both questionnaires (Table 2). The changes in SF-36 scores were

Table 3. Drug treatments received by those randomised to medical treatment at recruitment. Rates of satisfaction, acceptability and desire to continue the same treatment at four-month follow up. Values are given as *n* (%) of women. Progestogens: days 5–25 = 22 of 31 women, 12–25 = 9 of 31 women. HRT = hormone replacement therapy; NSAID = non steroidal anti-inflammatory drug.

	n = 94	Satisfied with treatment	Treatment acceptable	Continue treatment
Progestogens: days 12–25/5–25	31 (33)	10 (34)	11 (36)	6 (19)
Combined pill	24 (26)	8 (33)	8 (33)	6 (25)
Tranexamic acid	22 (23)	7 (34)	6 (29)	4 (18)
Danazol	15 (16)	5 (33)	7 (47)	3 (20)
HRT (with NSAID)	2 (2)	1 (50)	1 (50)	2 (100)

Table 4. Subsequent management of those followed up at two years. Values are given as *n* (%) of women.

	None	Medical	TCRE	Repeat TCRE	Hysterectomy	TCRE and hysterectomy
Medical (*n* = 86)	18 (21)	17 (20)	38 (44)	0	4 (4)	9 (10)
TCRE (*n* = 87)	65 (75)	7 (8)		6 (7)	5 (6)	4 (4)

Table 5. Menstrual status and symptoms at two-year follow up. Values are given as *n* (%) of women or mean [SD].

	Medical (*n* = 86)	TCRE (*n* = 87)	Difference (%)	95% CI for difference	*P*
Menstrual status					
No bleeding or very light	36 (42)	50 (58)	−16	−30 to −1	0·04
Unchanged or heavier	16 (18)	5 (6)	12	3 to 22	0·02
Duration of bleed (days)					
None	26 (30)	33 (38)	−8	−22 to 6	
1–3	7 (8)	14 (16)	−8	−16 to 4	0·5
3–5	45 (53)	31 (36)	17	−4 to 21	
> 5	8 (9)	9 (10)	−1	−8 to 20	
No. of days heavy bleeding	2·0 [2·8]‡	1·1 [1·3]‡	0·9	0·37 to 1·4	0·001
Bleeding score	6·8 [9·9]‡	5·4 [8·1]‡	−1·4	−1·4 to 4·1	0·33
Pain score	4·1 [7·4]‡	3·9 [7·5]‡	1·2	−2·1 to 2·4	0·9
Dysmenorrhoea: same or worse	25 (29)	20 (23)	6	−7 to 19	0·46
Dyspareunia: same or worse	9 (11)	5 (6)	5	−3 to 13	0·1
Premenstrual symptoms					
Breast discomfort	47 (58)*	49 (58)**	0	−17 to 13	0·96
Bloating	57 (70)	55 (65)**	5	−11 to 17	0·44
Irritability	55 (68)	47 (55)**	13	−5 to 25	0·09
Headaches	43 (53)*	34 (40)**	13	−4 to 26	0·09
Depression	30 (37)‡	28 (33)‡	4	−11 to 17	0·58

Asterisks/daggers denote changes from baseline (*$P < 0.05$, **$P < 0.01$, ‡$P < 0.001$).
Difference in means or proportions (%).
95% CI for difference = 95% confidence intervals for difference in means or proportions (%).

higher for all health scores at two years for those allocated TCRE, but not significantly so. Women in the medical arm scored better than at baseline and significantly so for five of the eight variables, and in addition there was an overall improvement from four-month scores. In the TCRE group seven of the eight health scores were significantly improved from baseline, but scores were lower than those obtained at four months. Figure 1 shows how the follow up scores compare with baseline and with normative values for a healthy female population of equivalent age[20]. The number of women who were taking time off work each month because of their periods was significantly, and comparably reduced from 30% at recruitment to 14% in the medical arm and 10% in the surgical arm at two years ($P = 0.1$, 95% CI of difference −5% to 15%).

Patient preference

The parallel, nonrandomised cohorts of women, characterised by a preference for medical treatment or TCRE, described previously[15], were not followed up by questionnaire at two years. Subsequent surgical treatment received at two years was determined for these women from the surgical database. Two women of the 19 in the preferred medical arm had had a TCRE, but no hysterectomies had been performed in this group of women. Of the 21 women

Table 6. Patient satisfaction, effectiveness and acceptability of treatment, and recommended treatment. Values are given as *n* (%) of women.

	Medical (*n* = 86)	TCRE (*n* = 87)	Difference (%)	95% CI for difference	*P*
Totally or generally satisfied with treatment	48 (57)	68 (79)	−22	−36 to −9	0·002
Cure or acceptable improvement in symptoms	53 (61)	69 (81)	−20	−31 to −4	0·017
Treatment acceptable	65 (77)	79 (93)	−16	−26 to −4	0·004
What treatment would you recommend to a friend?					
None	15 (17)	9 (11)			
Medical	21 (24)	2 (2)			
TCRE	40 (47)	68 (78)	−31	−45 to −18	<0·001
Hysterectomy	10 (12)	8 (9)			

95% CI for difference = 95% confidence intervals for difference in proportions (%).

in the preferred TCRE arm, eight had had a hysterectomy and one had had a repeat TCRE.

DISCUSSION

This study represents the longest follow up of women participating in a randomised trial of medical treatment for heavy menstrual loss. It is also the longest follow up of women undergoing TCRE who were not referred initially for surgical treatment of their periods. Its other strength is that the randomised cohorts are not distorted by motivational bias, as women preferring treatments were identified and studied separately from the outset. This has allowed us to observe the treatment progression in both cohorts in the knowledge that requests for TCREs from those in the medical arm have not resulted from 'resentful demoralisation'[21]: that is, disappointment at their initial allocation. Analysis was by intention-to-treat, and therefore no women changed trial arms or were withdrawn from the study because of subsequent treatments received.

Follow up questionnaires were not obtained from eight women in the medical arm and six in the TCRE arm, most of whom had left the region. Since this is the only hospital offering gynaecological services in the area, information was available on operative procedures, general practitioner correspondence, and subsequent clinic attendance for the women who remained in the region. It is unlikely that loss of 8% of the original participants has affected the generalisability of the results as the further surgical treatment received by these women was similar to those who were followed up.

Medical arm

Only 20% of women initially allocated to take medical treatment continued to take this at two years, although 41% of women in this group had avoided surgical treatment. Individual medical treatments used by women at follow up were not determined as it was the aim of the trial to evaluate a medical policy rather than identify optimal medical treatment. Stratified analysis on the basis of subsequent treatment received in the medical arm is also methodologically unsound, in view of the small numbers and inherent bias created as women chose their subsequent treatments. Satisfaction with, and acceptability of, treatment were much improved from four months, but remained significantly less than among those allocated to TCRE. Bleeding and pain scores were significantly less than at four months and were comparable to the TCRE arm. Other menstrual parameters were also significantly improved, but pelvic pain remained low and equivalent in both arms. These improvements from the four-month results may be due to the 59% of women in this arm who underwent TCRE or hysterectomy. Nevertheless, those women avoiding surgical treatment can be presumed to be equally satisfied as they were aware that surgery was available had they requested it. The fact that only 24% of women would recommend medical treatment, compared with 85% (40/47) of those who subsequently underwent TCRE in the medical arm, who would recommend TCRE, strengthens the argument that TCRE has improved the medical arm results.

Surgical arm

Of women in the TCRE arm, 17% had undergone surgical retreatment at two years, less than the proportion reported in previous randomised single-centre trials comparing TCRE with hysterectomy[1,2], but similar to that in the multi-centre Medical Research Council (MRC) trial[3]. These differences between the trials mounted in our centre may represent variation at recruitment in both severity of symptoms, and expectations of treatment, as women in the present trial were excluded from randomisation if they were seeking surgical treatment. Satisfaction with, and acceptability of, treatment remained high at about 80%, comparable to the four-month follow up, and significantly better than among women in the medical arm. This also correlated well with the numbers who would recommend TCRE (78%) as treatment for heavy menstrual loss. Bleeding and pain scores and number of heavy days remained highly significantly better than at recruitment, similar to four-month levels, with only the number of days heavy bleeding significantly less than among those in the medical arm. Premenstrual symptoms also remained significantly reduced from baseline but the effect had diminished in comparison with the four-month results. Importantly, women in the surgical arm did not have higher hysterectomy rates than those in the medical arm (10% *vs* 14%, 95% CI −16 to 4%), suggesting that early recourse to TCRE does not increase the risk of hysterectomy.

Health related quality of life

This trial represents the longest term evaluation of change in health related quality of life for women with heavy menstrual loss. It could be argued that this should be the definitive arbiter of treatment success, and its measurement was recommended by the effective health care group[4] for outcome assessment of treatments for menorrhagia. Heavy menstrual loss is known to cause significant deterioration in general health and quality of life[12–14] which has often been overlooked in the evaluation of treatment. The reduced SF-36 scores observed at baseline were consistent with the scores reported for other women with menorrhagia[13]. For women in the

TCRE arm, two-year health related quality of life scores, as measured by SF-36, remain at near normative levels[20], are significantly improved from baseline, and are similar to values obtained at two years post-TCRE by Sculpher *et al.*[2]. The scores are however, globally reduced from the four-month results. One possible explanation is an initial high score achieved in a honeymoon period occurring soon after relief of symptoms. Another is that there has been a genuine fall off in the benefits of the operation, although this is not borne out by the satisfaction and menstrual status results. Women in the medical arm also had higher SF-36 scores than at baseline, but these remained lower than scores achieved in the TCRE arm and substantially lower than normative values (Fig. 1). The increased scores in the medical arm from the four-month data may reflect the number of women undergoing surgical treatment since then.

Patient preference

Women who had exhibited a preference and chosen their treatments were not followed up by questionnaire at two years because of the small numbers involved and the difficulties of analysing data from these nonrandomised observational cohorts. Nonetheless, subsequent treatments received were determined from hospital records. These confirmed the conclusions of the four-month follow up data. Those preferring TCRE had a markedly higher re-operation rate than among those randomised to TCRE (42% *vs* 17%). This is likely to reflect different expectations of treatment among those preferring surgical treatment[15] and indicates that these should be clearly determined at outset, with hysterectomy discussed with women wanting amenorrhoea. In contrast, of the 19 women preferring medical treatment, only two had undergone TCRE and none a hysterectomy, a much lower proportion than those randomised to medical treatment (54% TCRE, 14% hysterectomy). This confirms that those women with a preference for medical treatment have a good chance of avoiding surgery, and can be encouraged to pursue this option.

CONCLUSION

At two years, women allocated to TCRE are still in better health than those initially managed medically. The results therefore consolidate the conclusions drawn from the four-month data. The findings apply to women seen by a gynaecologist for the first time for treatment of heavy menstrual loss, and who do not have a treatment preference. Early recourse to hysteroscopic surgery will afford these women better relief of symptoms and improvements in health related quality of life. Reassuringly, over 80% of those managed by TCRE at the outset have avoided further surgical treatment and there was no detectable increase in hysterectomy rates at two years in this group compared with those randomised to medical therapy. Nevertheless, 41% of women in the medical arm have not undergone surgical treatment for their complaint, although only half of them continue to take any medical therapy. Less invasive surgical techniques, such as microwave ablation[22] or thermal balloon[23,24] as alternatives, should now be evaluated in well constructed randomised trials, comparing them with hysteroscopic endometrial ablation, before accepting them as effective alternative management for menorrhagia. Results from two small randomised trials comparing the Mirena coil with TCRE are available which demonstrate a significantly greater reduction in pictorially assessed blood loss[25] following TCRE[26,27]. Larger randomised studies comparing the Mirena coil and TCRE, with longer follow up, are required to demonstrate meaningful differences in outcome other than pictorially assessed blood loss.

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